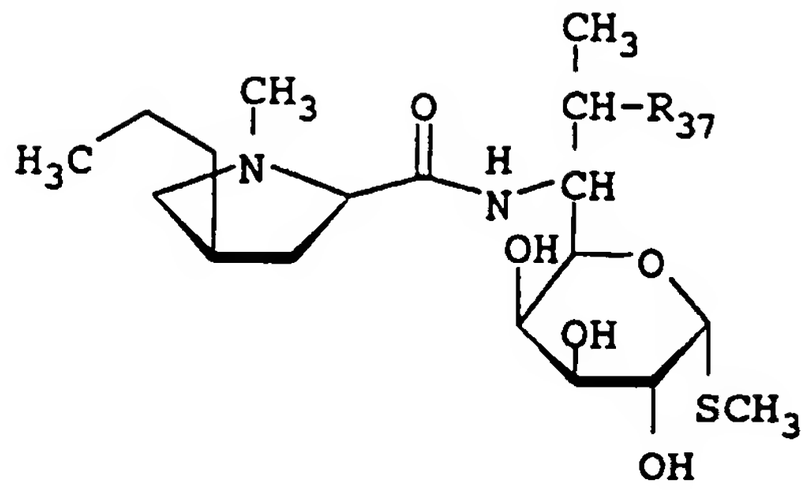
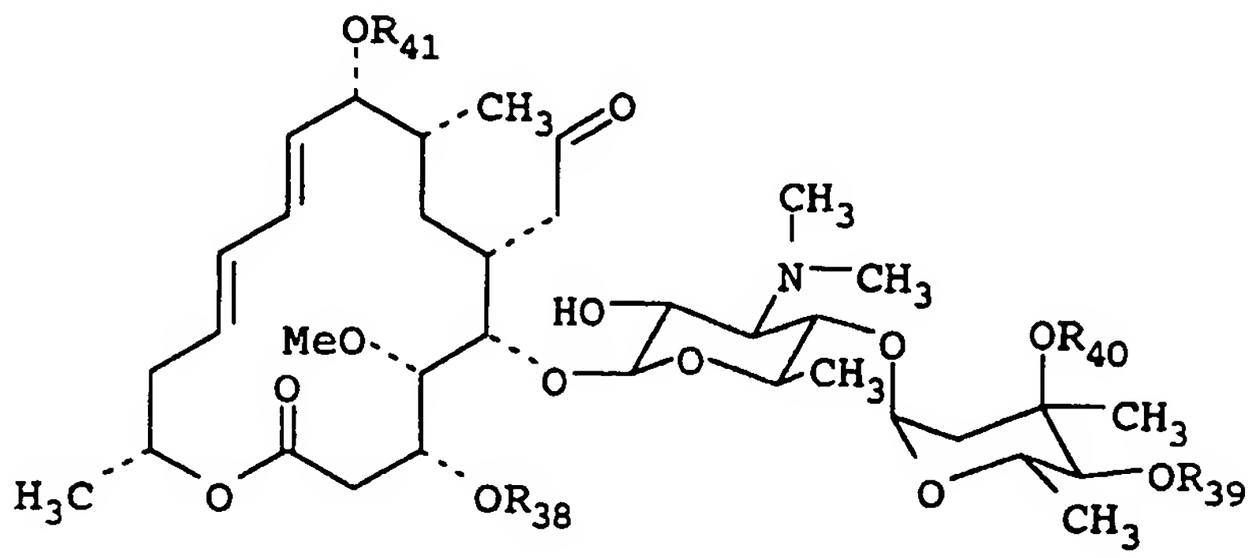


wherein:

R_{37} is selected from the group consisting of Cl and -OH;

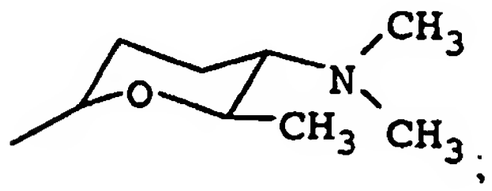
xvi)



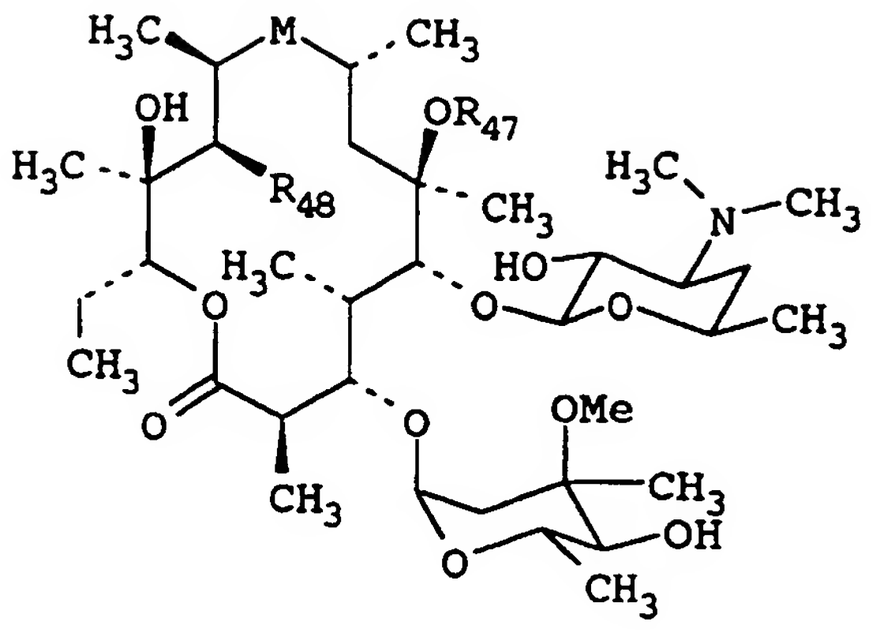
wherein:

R_{38} R_{39} R_{40} are independently selected from the group consisting of H and acyl; preferably they are selected from the group consisting of H acetyl, propionyl, butyrryl, valeryl

R_{41} is independently selected from the group consisting of H and



xvii)

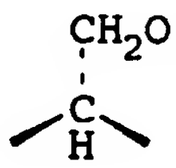


wherein:

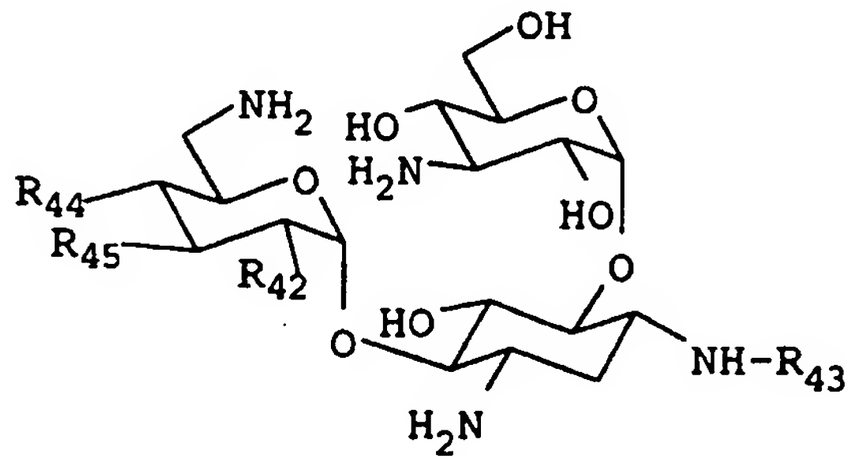
R_{47} is selected from the group consisting of H and $-CH_3$

M is selected from the group consisting of CO, N-methyl-aminomethylene and $-CH(NHR_{49})-$ wherein R_{49} is a substituted methylene bridge connecting N with R_{48}

R_{48} is hydroxyl or, when **M** is $-CH(NHR_{49})-$, is -O-;

Preferably R_{49} is  ;

xvii)



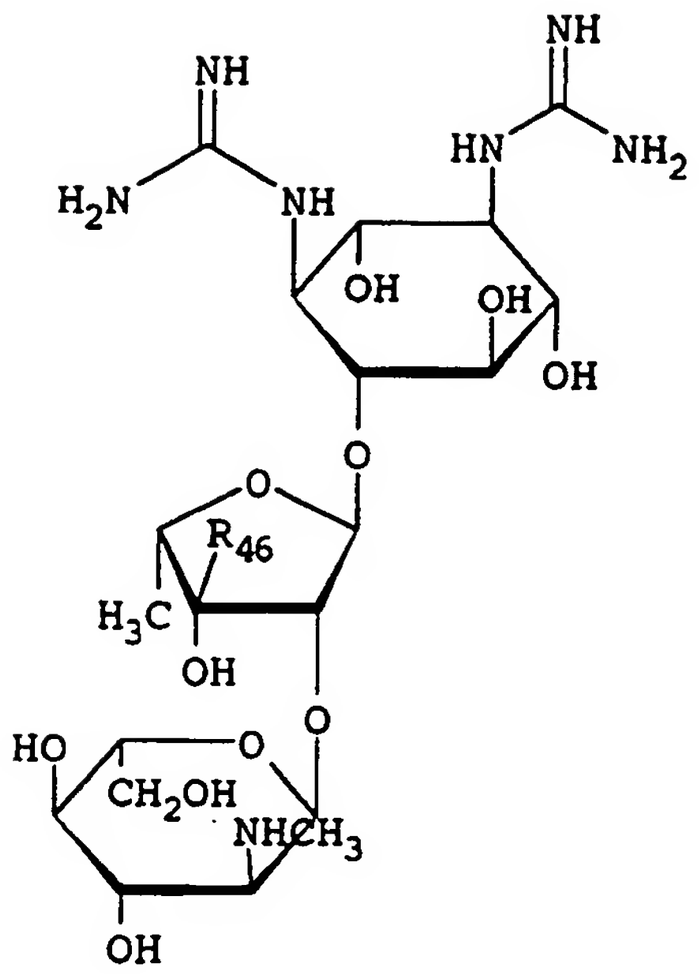
wherein:

R_{42} is selected from the group consisting of hydroxyl and amino;

R_{43} is selected from the group consisting of hydrogen, (R) and (S)-4-amino-2-hydroxybutyrryl

R_{44} and R_{45} are independently selected from the group consisting of hydrogen and hydroxyl.

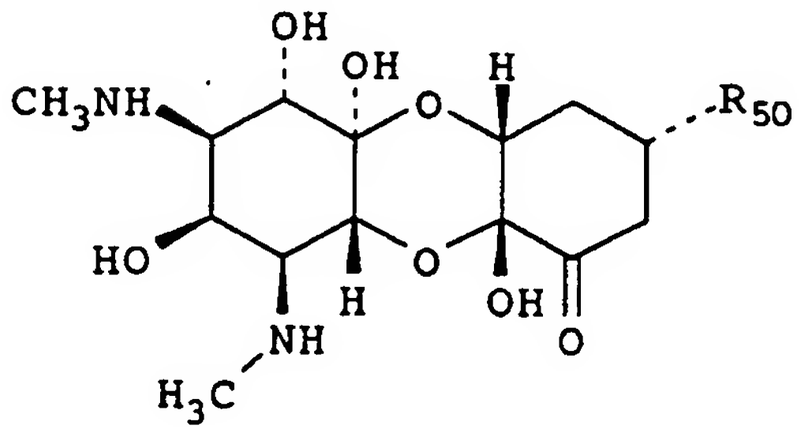
xviii)



wherein:

R_{46} is selected from the group consisting of $-CH_2OH$ and $-CHO$;

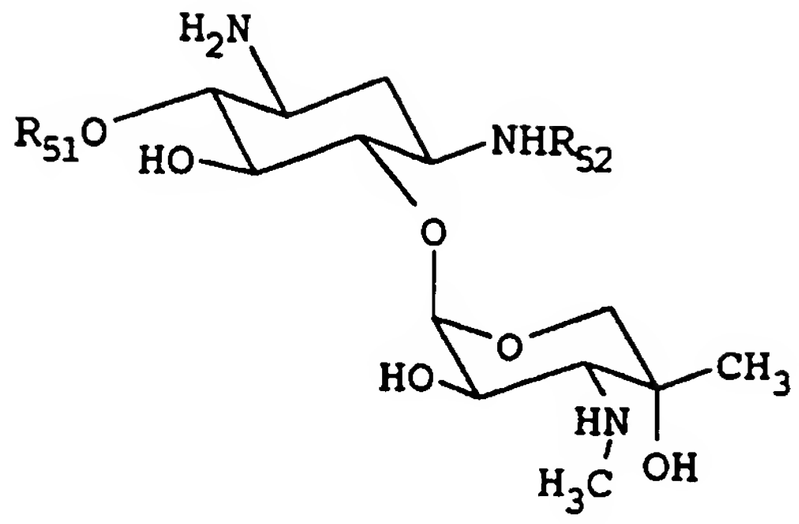
xix)



wherein:

R_{50} is a C_1-C_4 alkyl, preferably it is selected from the group consisting of methyl and n-butyl.

xx)

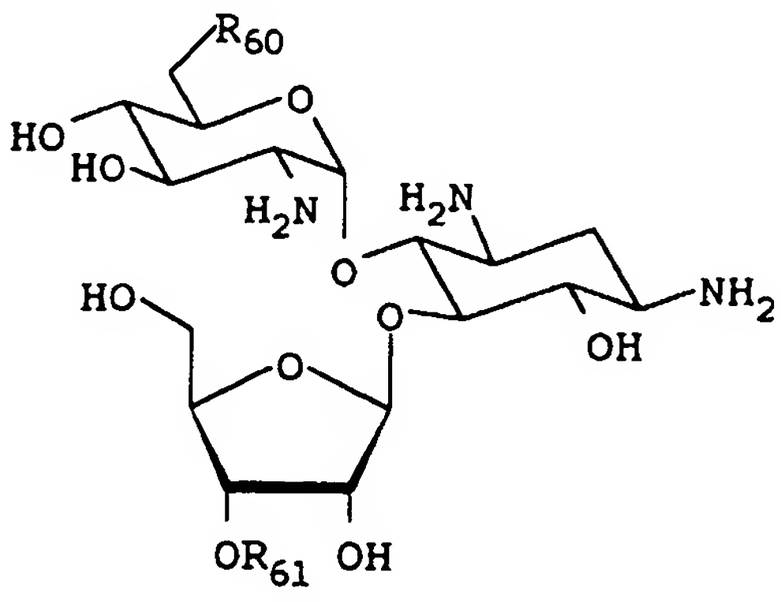


wherein:

R_{51} is independently selected from the group consisting of 3-amino-6-(aminomethyl)-3,4-dihydro-2H-pyran-2-yl and 2-amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-eritro-hexopyranosyl,

R_{52} is selected from the group consisting of H and $-CH_2CH_3$.

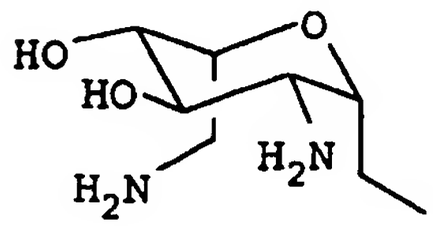
xxi)



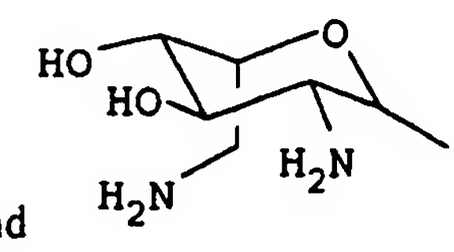
wherein:

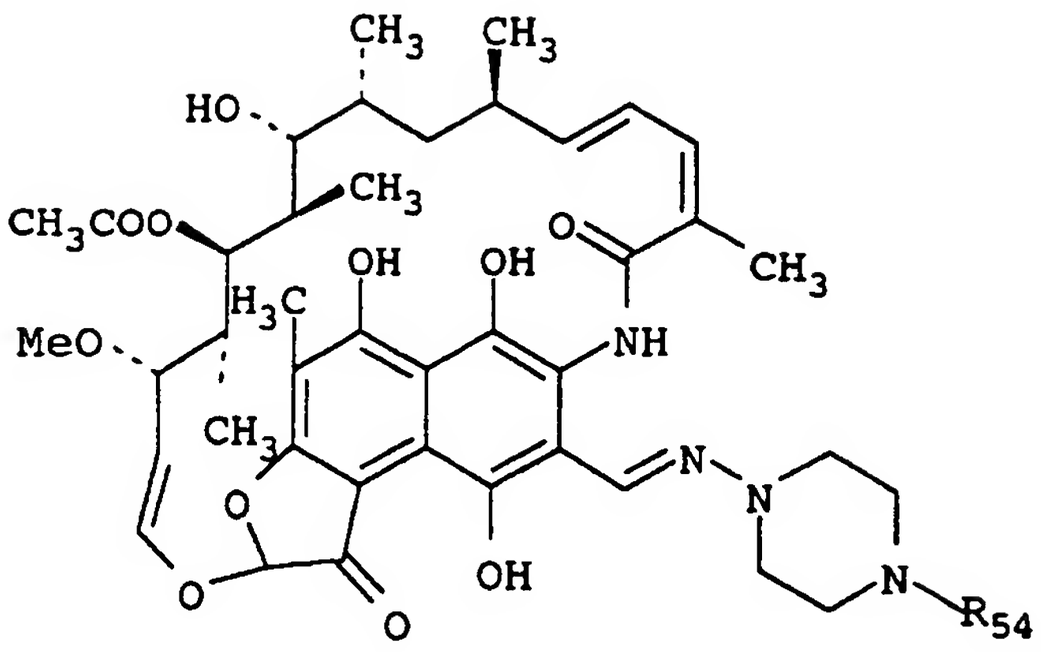
R_{60} is selected from the group consisting of –OH and $–NH_2$;

R_{61} is selected from the group consisting of H,



and





wherein R_{54} is a C_1-C_4 linear or cyclic alkyl, preferably it is selected from the group consisting of methyl and cyclopropyl.

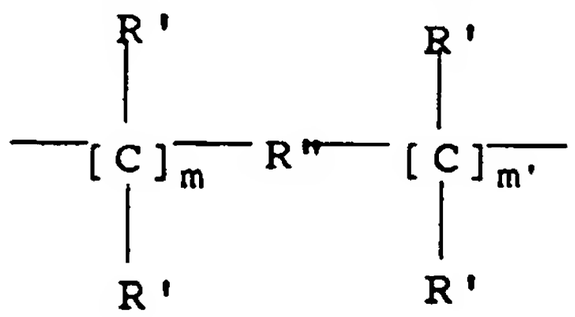
In a preferred embodiment **X** is a divalent radical having the following structure : $(L')_f$-X', wherein

X' is a divalent radical comprising from 1 to 50 carbon atoms, from 0 to 10 nitrogen atoms, from 0 to 20 oxygen atoms, from 0 to 2 sulfur atoms and from 0 to 8 halogen atoms.

L' is selected from the group consisting of O, S, NR' and CO; with **R'** selected from the group consisting of H and linear and branched C_1-C_4 alkyl;

f is 0 or 1.

In a preferred embodiment X' is represented by the following formula:



wherein:

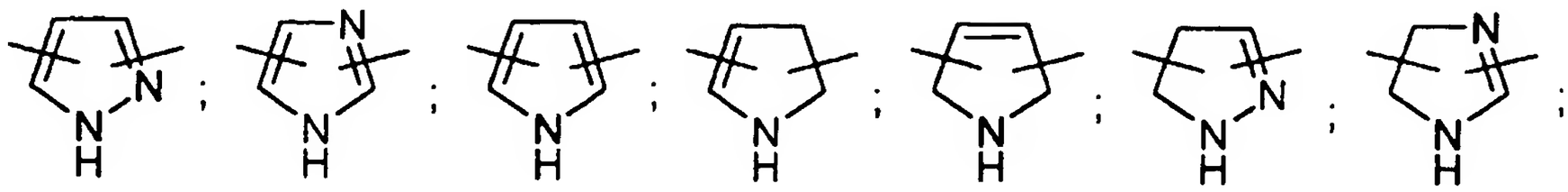
m is selected from 0, 1, 2 and 3; preferably it is 1;

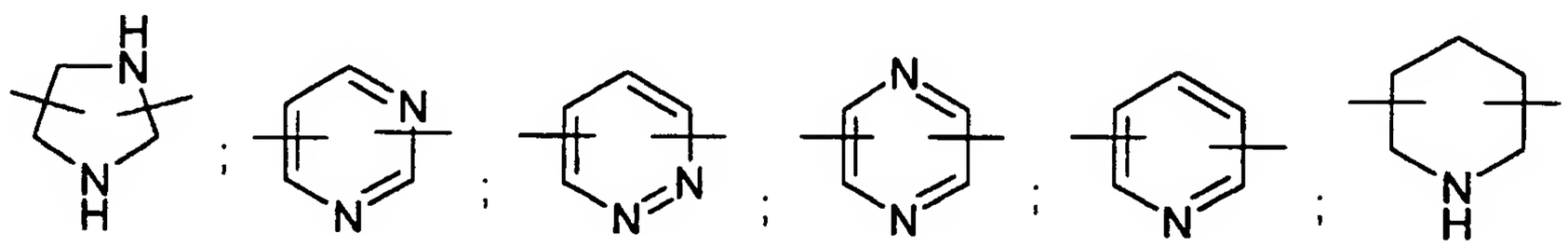
m' is selected from 1, 2 and 3; preferably it is 1;

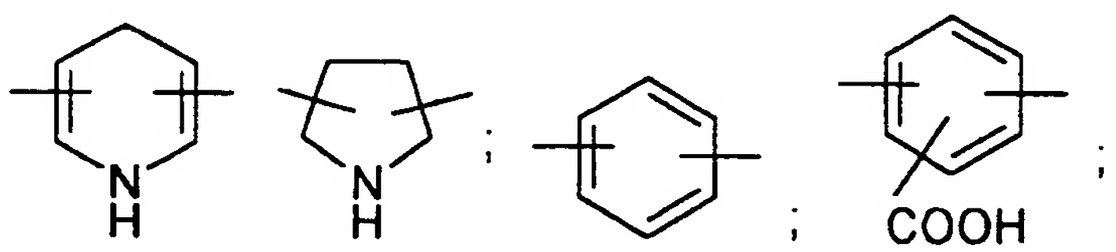
each **R'** is independently selected from the group consisting of H, linear and branched C_1-C_4 alkyl; preferably it is H;

R" is selected from the group consisting of: 5 and 6 membered saturated, unsaturated and aromatic heterocycles, phenyl, optionally substituted by a carboxylic group;

When R" is an heterocycle, it is preferably selected from the group consisting of the following divalent radicals:







More preferably R" is selected from the group consisting of a pyridyl and pyrazolyl radical , most preferably it is selected from the group consisting of 2,3-, 2,6- pyridyl and 3, 5-pyrazolyl radicals, wherein 2, 3, 5 and 6 indicate the positions connecting the ring to the carbons of the bridge.

In another preferred embodiment X' is a C_1-C_{20} alkylene group, preferably C_2-C_6, optionally substituted by - NH_2, -OH, $NHCOR^E$ wherein R^E is selected from the group consisting of methyl, ethyl, linear or branched C_3-C_5 alkyl; a C_5-C_7 cycloalkylene group, optionally substituted by one or more C_1-C_6 alkyl chains;

In a third preferred embodiment X' is selected from the group consisting of a group of formula :

-CHR'''-CHR'''-(O-CHR'''-CHR''')$_p$- and -CHR'''-CHR'''-CHR'''-(O-CHR'''-CHR'''-CHR''')$_p$-

wherein each **R'''** is independently selected from the group consisting of H and CH_3

p varies from 1 to 6, preferably from 1 to 4.

In another preferred embodiment the group X comprises a radical having specific antioxidant properties as disclosed in WO 00/61537, WO 00/61541, WO 00/61604.

Non limiting examples of compounds from which the antioxidant radical is derived are: Aspartic acid, Histidine, 5-Hydroxytryptophan, 4-Thiazolidincarboxylic acid, 2-Oxo-4-thiazolidincarboxylic acid, 2-Thiouracil, 2-Mercaptoethanol, Esperitine, Secalciferol, 1-α-OH-vitamin D2, Flocalcitriol, 22-Oxacalcitriol, 24,28-Methylene-1α-hydroxyvitamin D2, 2-Mercaptoimidazol, Succinic acid,

L-Carnosine, Anserine, Selenocysteine, Selenomethionine, Penicillamine, N-Acetylpenicillamine, Cysteine, N-acetyl-cysteine, Glutathione or its esters, Gallic acid, Ferulic acid, Gentisic acid, Citric acid, Caffeic acid, Hydrocaffeic acid, p-Coumaric acid, Vanillic acid, Chlorogenic acid, Kynurenic acid, Syringic acid, Nordihydroguaiaretic acid, Quercetin, Cathechin, Kaempferol, Sulphurethyne, Ascorbic acid, Isoascorbic acid, Hydroquinone, Gossypol, Reductic acid, Methoxyhydroquinone, Hydroxyhydroquinone, Propyl gallate, Saccharose, Vitamin E, Vitamin A, 8-Quinolol, 3-ter-Butyl-4-hydroxyanisole, 3-Hydroxyflavone, 3,5-ter-Butyl-p-hydroxytoluene, p-ter-Butyl-phenol, Timolol, Xibornol, 3,5-di-ter-Butyl-4-hydroxybenzyl-thioglycolate, 4'-Hydroxybutyranilide, Guaiacol, Tocol, Isoeugenol, Eugenol, Piperonyl alcohol, Allopurinol, Conyferyl alcohol, 4-Hydroxyphenetyl alcohol, p-Coumaric alcohol, Curcumin, N,N'-Diphenyl-p-phenylenediamine, Ethoxyquin, Thionine, Hydroxyurea, 3,3'-Thiodipronic acid, Fumaric acid, Dihydroxymaleic acid, Thioctic acid, 3,4-Methylendioxycinnamic acid, Piperonylic acid, N-Ethylendiethanolamine, Thiodiethylenglycol.

The following are non-limiting example which illustrate the invention.

Experimental

Example 1

Male Guinea pigs (weighing 300 to 500 g) were killed by a blown on the neck and exsanguinated. Urinary bladders were cut into strip preparations (3x12 mm). Guinea-pig bladder strips were rapidly transferred to jacketed tissue baths (25 ml) and mounted between two hooks. One the hooks was connected to a force transducer (Gould UC2). The strips were maintained at 37°C in a physiological salt solution. (PSS) that contains the following components: NaCl (119 mM), KCl (4.6 mM), $CaCl_2$ (1.5 mM), $MgCl_2$ (1.2 mM), $NaHCO_3$ (20 mM), NaH_2PO_4 (1.4 mM) and glucose (11 mM).The solution was gassed with a 95/5 mixture of O_2/CO_2 until a pH of 7.4 was achieved. A tension of 0.5 g was initially applied to each preparation. During stabilization (40-60') the strips were repeatedly washed and the tension was adjusted. Tissue contraction was induced by corbachol $3x10^{-6}$ M.

The experiment compares the inhibition of contraction obtained by using a solution of the composition according to the invention with the effect achieved by the same drug without cyclodextrin. Both the composition and the drug were dissolved in dimethylsulphoxyde (DMSO) and then added to the tissue bath were the their concentration was $1.0x10^{-5}$ M.

The drug used is 2-fluoro-α-methyl[1,1'-biphenyl]-4-acetic acid 4-(nitrooxy) butyl ester (NO-1).

F1and F2 represent the following compositions:

F1: 1.340 g of α CD and 0.500 g of NO-1 mixed in in water and then dried.

F2: 1.820 g of dimethyl β CD and 0.500 g of NO-1 mixed in water and then dried.

F0 represents the comparative test performed by using NO-1 alone (no CD).

The percentage of inhibition of contraction obtained were the following:

Composition	Inhibition (%)
F1	26.05
F2	31.52
F0 (comparative)	21.67

Example 2

Male Guinea pigs (weighing 300 to 500 g) were killed by a blown on the neck and exsanguinated. The thoracic aorta artery was isolated, placed in a ice cold PPS that contains the following components: NaCl (119 mM), KCl (4.6 mM), $CaCl_2$ (1.5 mM), $MgCl_2$ (1.2 mM), $NaHCO_3$ (20 mM), NaH_2PO_4 (1.4 mM) and glucose (11 mM), cleaned of connective tissue and cut into transverse ring (3mm). Each ring was then suspended vertically in the organ chamber (25 ml) and mounted between two hooks in PPS maintained at 37°C and gassed with a mixture 95/5 of O_2/CO_2 until achievement of a pH 7.4. One of the hooks was connected to a force transducer (Gould UC2). A resting tension of 2 g was initially applied to each preparation. During stabilization (45') the strips are repeatedly washed and the resting tension is adjusted.

Aorta rings were precontacted with phenylephrine $3x10^{-6}$ M and exposed to the drug at a concentration $1.0x10^{-6}$ M.

The experiment compares the inhibition of contraction effect achieved by using a solution of the composition according to the invention with the effect achieved by the same drug without cyclodextrin. Both the composition and the drug were dissolved in dimethylsulphoxyde (DMSO).

The drug used is 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester (NO-2).

F1, F2 and F3 represent the following compositions:

F1: 1.470 g of α CD and 0.500 g of NO-2 mixed in water and then dried.

F2: 1.470 g of α CD and 0.500 g of NO-2 mixed in ethanol/water and then dri ed.

F3: 2.000 g of dimethyl β CD and 0.500 g of NO-2 mixed in water and then dried.

F0 represents the comparative test performed by using NO-2 alone (no CD).

The percentages of inhibition obtained were the following:

Composition	Inhibition (%)
F1	54
F2	59
F3	61
F0 (comparative)	19

5

Claims

1. Composition comprising cyclodextrins and a NO-releasing drug of formula

$$A\text{-}X\text{-}L\text{-}NO_n$$

wherein **A** is the radical deriving from a drug;

X is a divalent radical connecting A with the NO-releasing group $L\text{-}NO_n$;

L is selected from the group consisting of: O, S and NH;

n is 1 or 2.

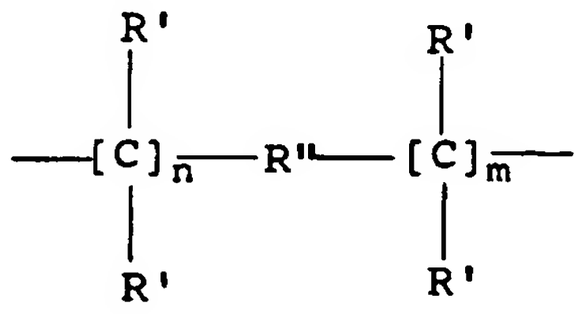
2. Composition according to claim 1 wherein $-L\text{-}NO_n$ is $-O\text{-}NO_2$

3. Composition according to claims 1-2 wherein the cyclodextrin is selected from the group consisting of α CD, dimethyl α CD, trimethyl-α CD, β CD, dimethyl-β CD, trimethyl-β CD, 2-hydroxypropyl-β CD, 3-hydroxypropyl-β CD, 2,3-dihydroxypropyl-β CD, γ CD, dimethyl γ CD, trimethyl γ CD and polymeric CD.

4. Composition according to claim 1-3 wherein the drug is selected from the following compounds: non steroidal antiinflammatory and analgesic drugs, antibacterial (antibiotics), antiviral, steroids, antineoplastic, β-adrenergics (agonists and blockers), antihyperlipoproteinemic, bone resorption inhibitors.

5. Composition according to claim 1-4 wherein **X** is a divalent radical having the following structure: $(L')_f\text{-}X'$, wherein **X'** is a divalent radical comprising from 1 to 20 carbon atoms, from 0 to 5 nitrogen atoms, from 0 to 5 oxygen atoms, from 0 to 2 sulfur atoms and from 0 to 5 halogen atoms and **L'** is selected from the group consisting of O, S, NR', CO, with **R'** selected from the group consisting of H, linear and branched C_1-C_4 alkyl; **f** is 0 or 1

6. Composition according to claim 5 wherein X' is represented by the following formula:



wherein:

n is selected from 0, 1, 2 and 3; preferably it is 1;

m is selected from 1, 2 and 3; preferably it is 1;

each **R'** is independently selected from the group consisting of H, linear and branched C_1-C_4 alkyl; preferably it is H;

R'' is selected from the group consisting of: 5 and 6 membered saturated, unsaturated and aromatic heterocycles, phenyl, optionally substituted by a carboxylic group.

7. Composition according to claim 5 wherein X' is a C_1-C_{20} alkylene group, preferably C_2-C_6, optionally substituted by - NH_2, -OH, $NHCOR^E$ wherein R^E is selected from the group consisting of methyl, ethyl, linear or branched C_3-C_5 alkyl; a C_5-C_7 cycloalkylene group, optionally substituted by one or more C_1-C_6 alkyl chains;

8. Composition according to claim 5 wherein X' is selected from the group consisting of a group of formula :

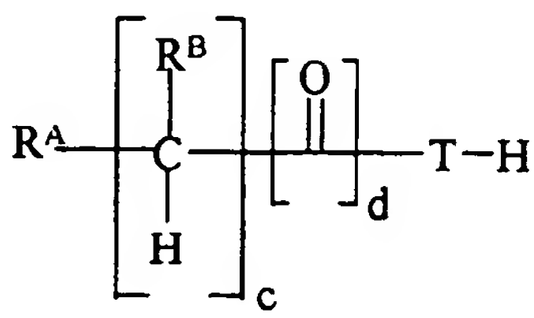
-CHR'''-CHR'''-(O-CHR'''-CHR''')$_p$- and -CHR'''-CHR'''-CHR'''-(O-CHR'''-CHR'''-CHR''')$_p$-

wherein each **R'''** is independently selected from the group consisting of H and CH_3

p varies from 1 to 6, preferably from 1 to 4.

9. Composition according to claims 1-8 wherein the drug is selected form the following formulas

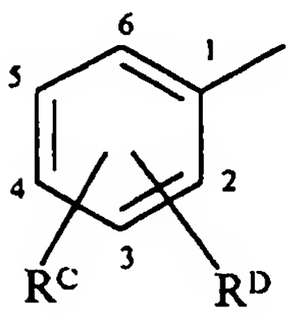
i)

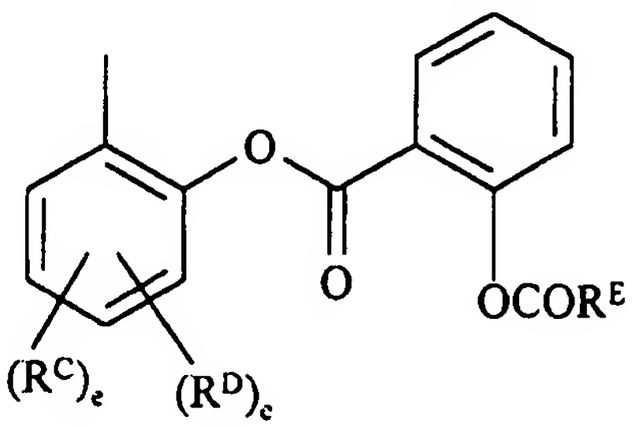


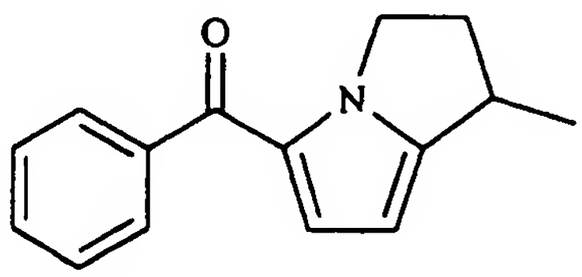
where **c** and **d** are independently 0 or 1;

T is selected from the group consisting of: O, NH and S;

$\mathbf{R^B}$ is selected from the group consisting of H, a linear or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl; When **c** is equal to 0 , **d** is 1, $\mathbf{R^A}$ is selected from the group consisting of:







wherein:

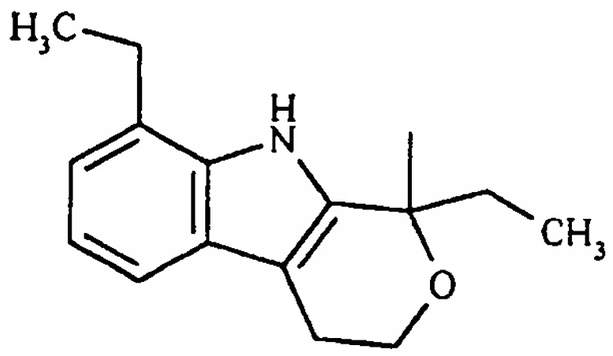
$\mathbf{R^C}$ is selected from the group consisting of amino, R^ECONH-, $OCOR^E$ group, and the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from the group consisting of O, N, and S;

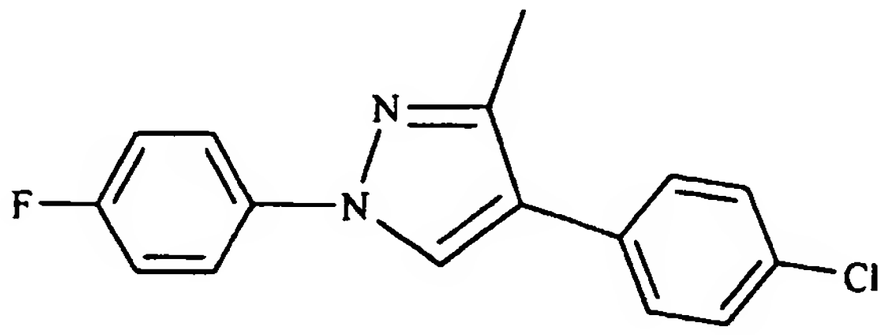
$\mathbf{R^E}$ is selected from the group consisting of methyl, ethyl and a linear or branched C_3-C_5 alkyl;

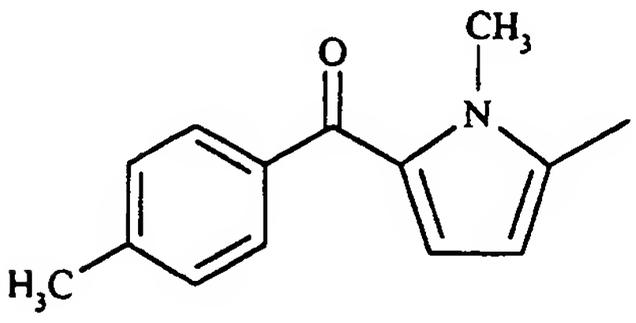
$\mathbf{R^D}$ is H, OH, halogen, a linear or when permissible branched alkyl having 1 to 4 atoms, a linear or when permissible branched alkoxyl having 1 to 4 atoms, a linear or when permissible branched perfluoroalkyl having 1 to 4 carbon atoms, for example trifluoromethyl, amino, mono- or di-(C_1-C_4) alkylamino;

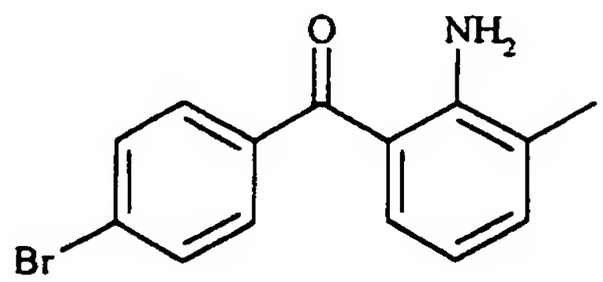
e is 0 or 1;

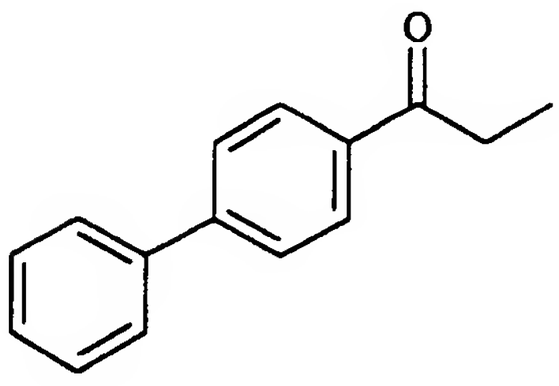
when **c** is equal to 1, **d** is equal to 1, $\mathbf{R^B}$ is hydrogen, $\mathbf{R^A}$ is selected from the group consisting of:

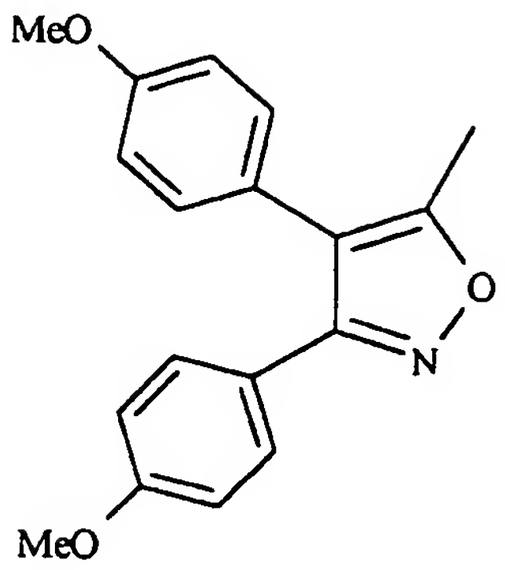


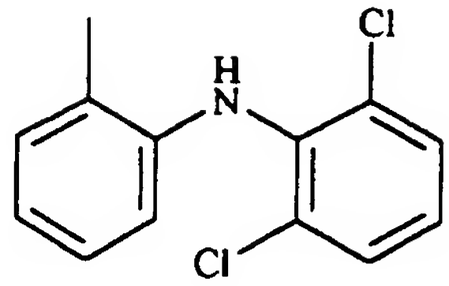


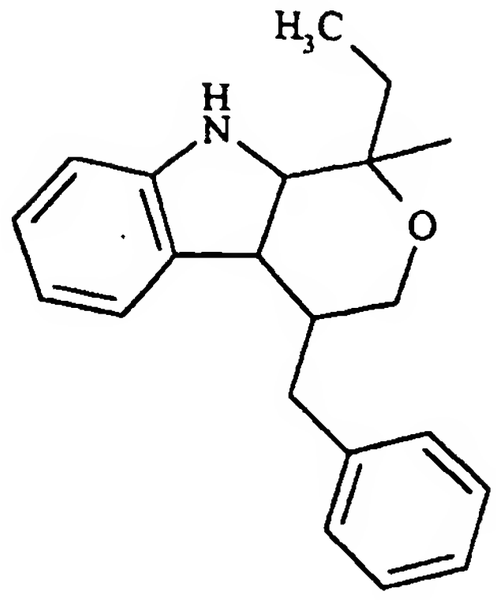


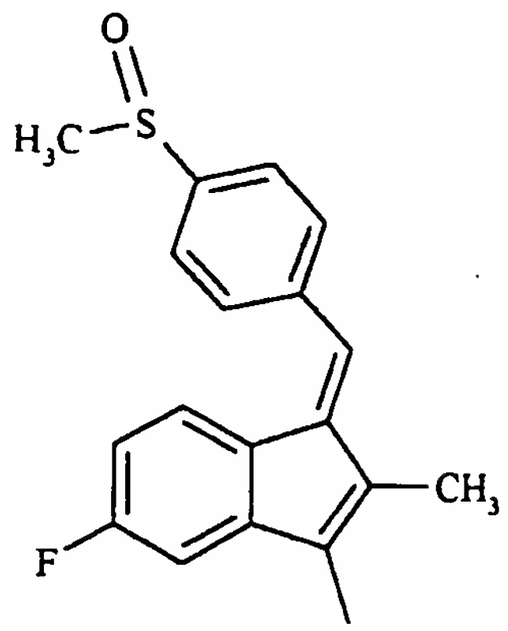


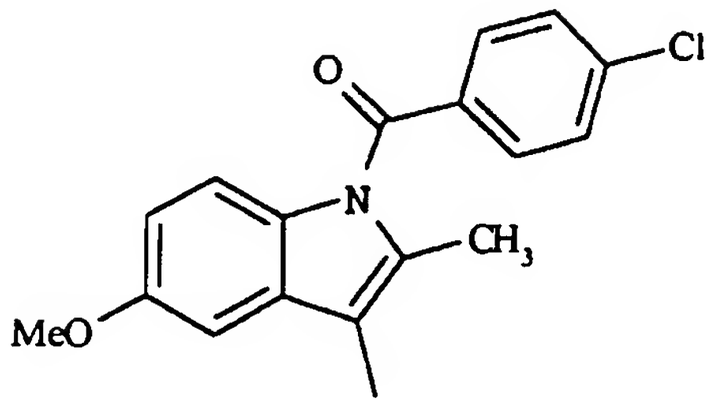




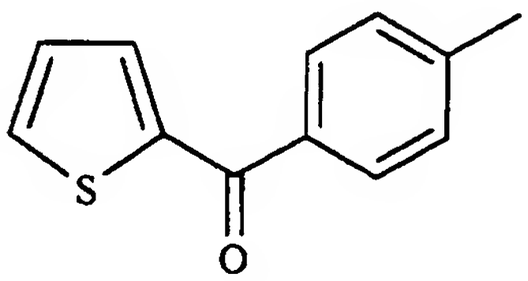


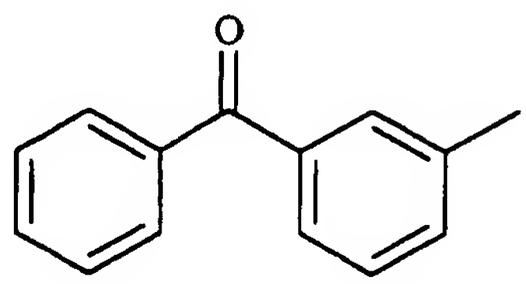


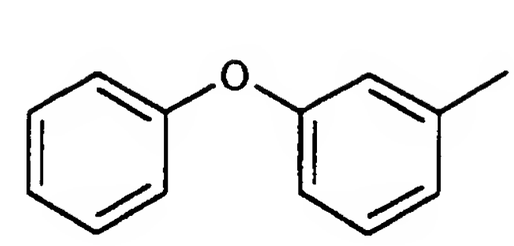


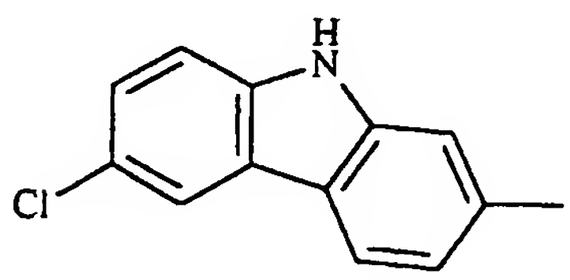


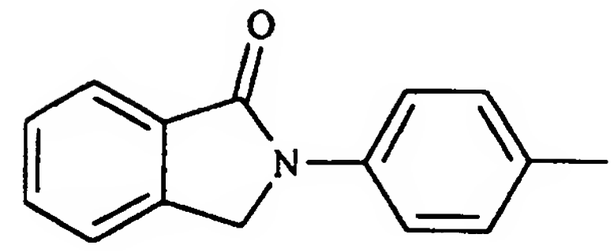
when **c** is equal to 1, **d** is equal to 1 and $\mathbf{R}^B$ is CH_3, $\mathbf{R}^A$ is selected from the group consisting of:

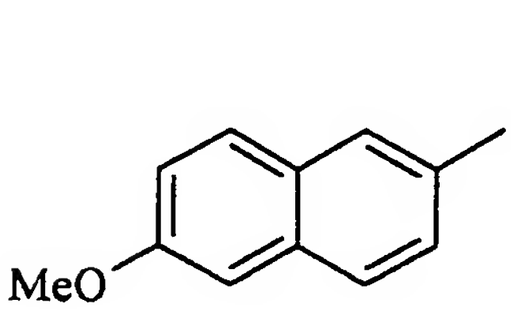


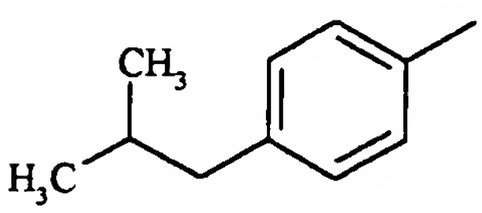


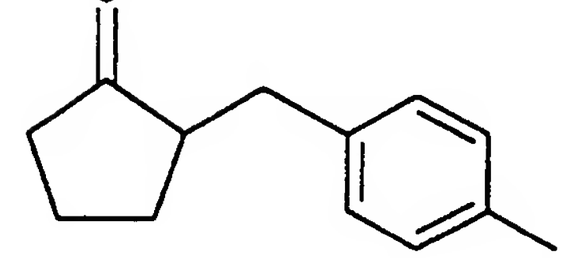


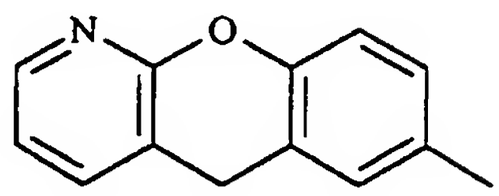


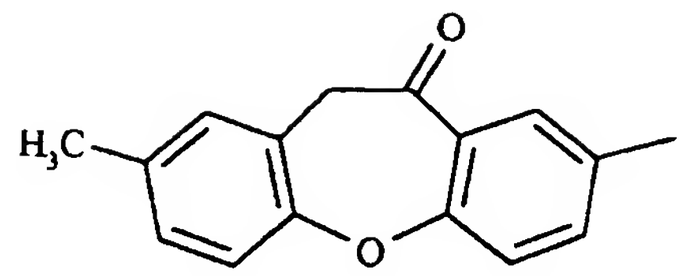


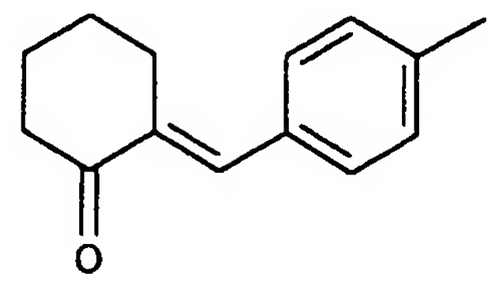


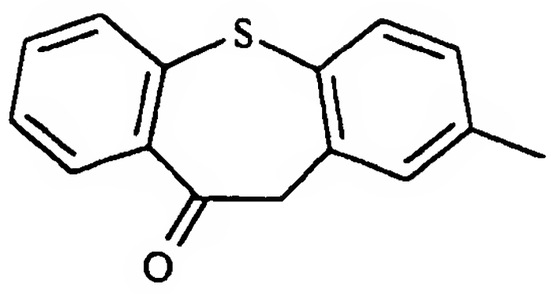


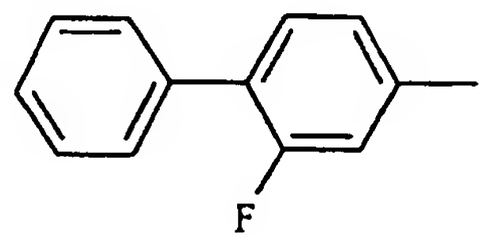




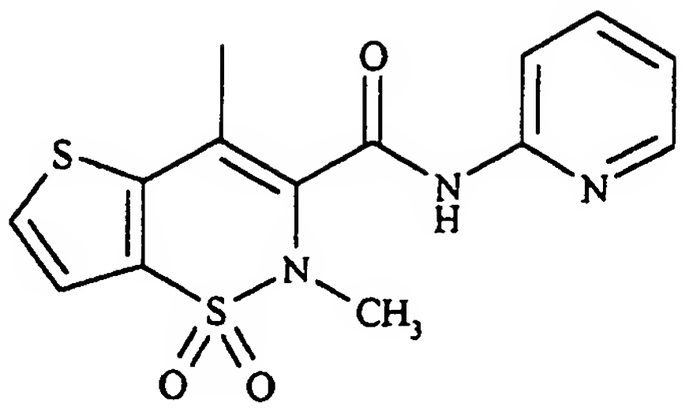


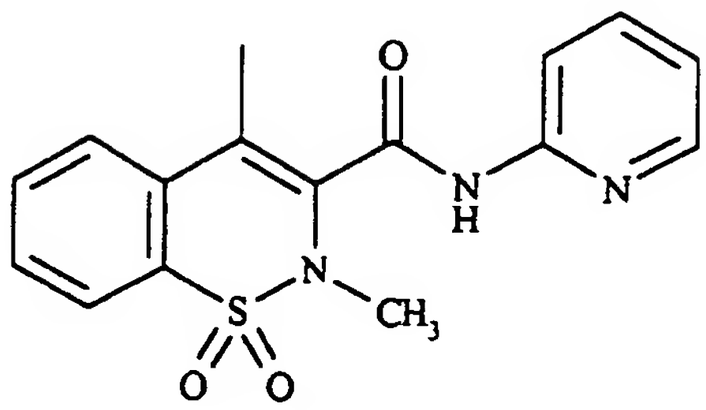


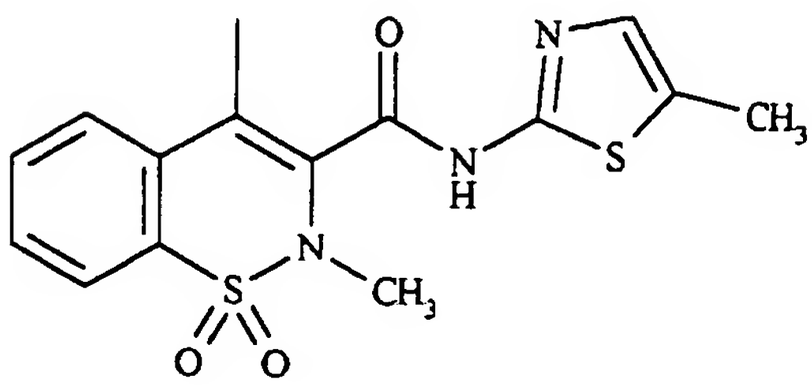


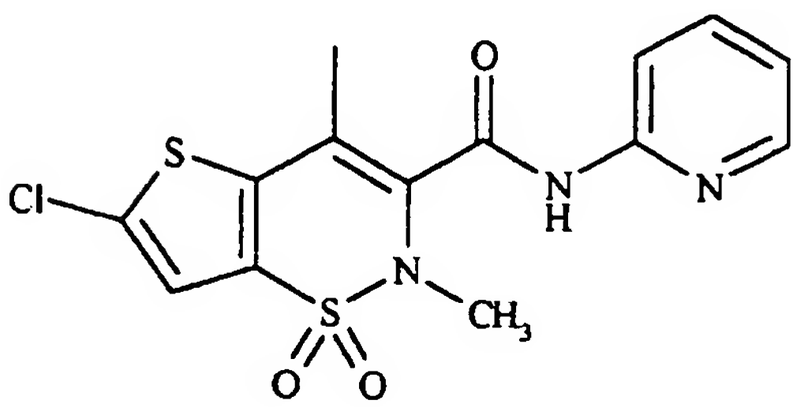


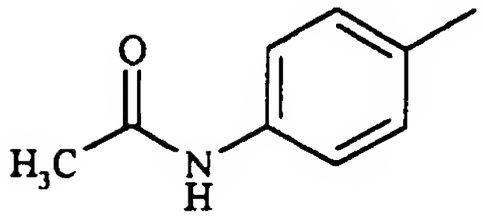
when **c** is equal to 0, **d** is equal to 0, $\mathbf{R^A}$ is selected from the group consisting of:

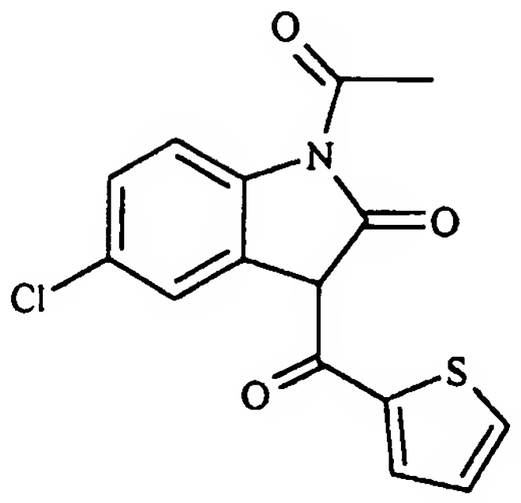






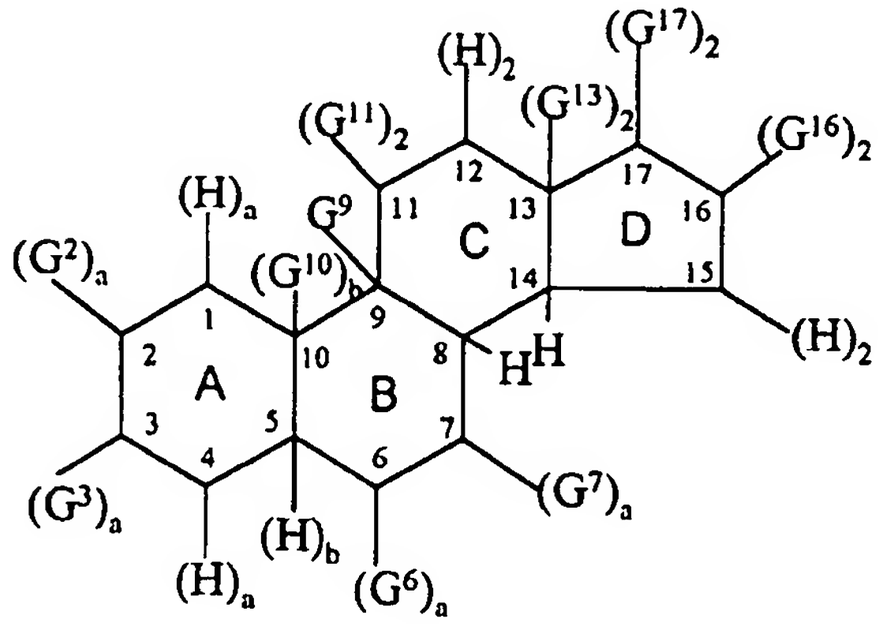






5

ii)



wherein:

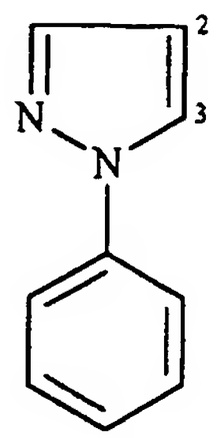
10 at the position 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 5-10 there may be a double bond; the ring A is optionally an aromatic ring;

a is equal to 1 or 2, **b** is equal to 0 or 1;

each G^2 is independently selected from the group consisting of H, Cl, Br;

each G^3 is independently selected from the group consisting of H, O-CH_3, O-CH_2-CH_2-Cl, OH; two G^3 can form a carbonyl group with the C^3 atom;

one G^2 and one G^3 can unite to form a ring of formula



wherein C^2=C^3 are part of the steroid structure;

each G^6 is independently selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^7 is independently selected from the group consisting of H, Cl, OH;

each G^9 is independently selected from the group consisting of H, Cl, F;

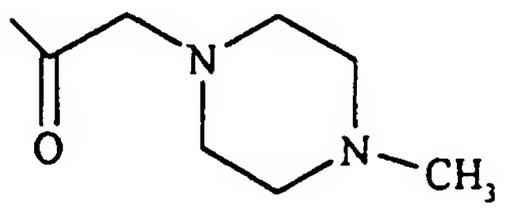
G^{10} is selected from the group consisting of H, Cl, F, CH_3, -CHO;

each G^{11} is independently selected from the group consisting of H, OH, , Cl; two G^{11} can form a carbonyl group with the C^{11} atom;

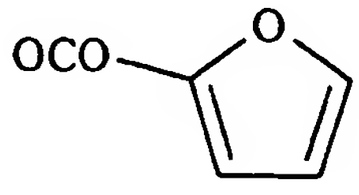
each G^{13} is independently selected from the group consisting of H, CH_3;

each G^{16} is independently selected from the group consisting of H, CH_3, OH; two G^{16} can form a vinyl group with the C^{16} atom;

each G^{17} is independently selected from the group consisting of H, OH and a monovalent radical comprising from 1 to 20 carbon atoms and from 0 to 5 oxygen, sulfur, nitrogen, halogen atoms; preferably it is H, OH, CH_3, C≡CH, CO-R-OH, CO-RH, CO-R-Cl, OCO-RH, CO-COO-RH, R-COOH, CH(OH)R-OH, COO-R-Cl, OC(O)O-RH, CO-R-SH, CO-R-O-CO-R-$N(CH_2CH_3)_2$, CO-SCH_2F, CO-R-OCORH,



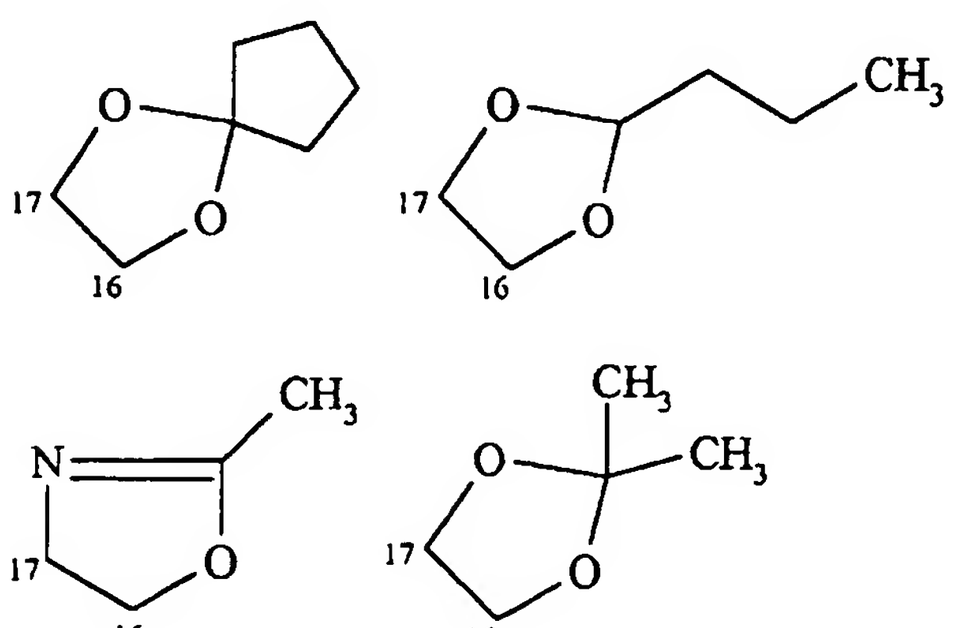
wherein R is a C_1-C_{20} linear or branched alkylene radical, and



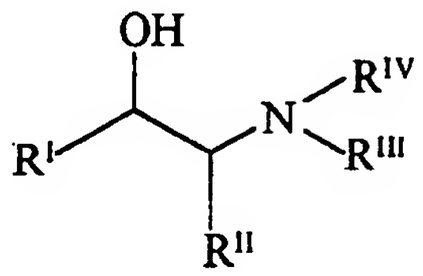
;

two G^{17} can form a carbonyl group with the C^{17} atom;

one G^{16} can unite with a G^{17} group to form, together with C^{16} and C^{17} the following groups:



iii)



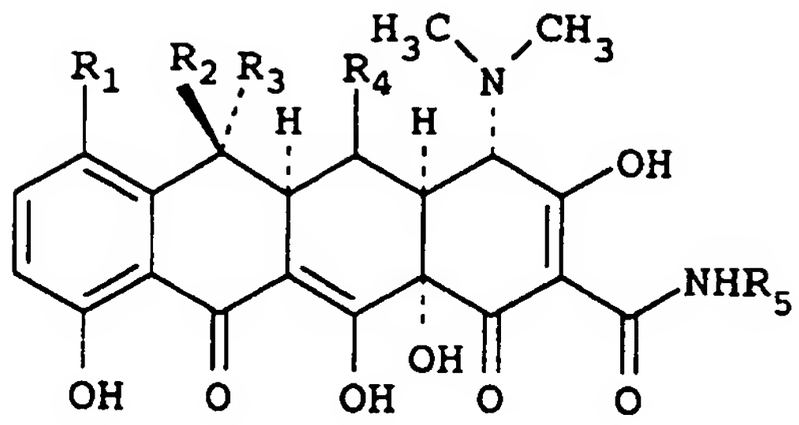
R^I is monovalent radical comprising from 6 to 20 carbon atoms and from 0 to 6 heteroatoms selected from oxygen, nitrogen, sulfur, chlorine, bromine, fluorine;

R^{II} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms;

R^{III} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms;

R^{IV} is selected from the group consisting of hydrogen, a linear or branched alkyl having from 1 to 4 carbon atoms and a substituted aryl; preferably R^{IV} is selected from the group consisting of tert-butyl and isopropyl;

iv)



wherein:

R_1 is selected from the group consisting of H, Cl and dimethylamino,

R_2 is selected from the group consisting of H, OH,

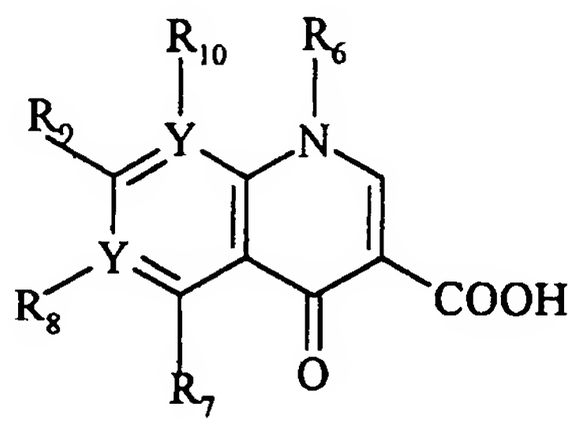
R_3 is selected from the group consisting of H, CH_3,

R_2 and R_3 together can be a methylene group (CH_2=),

R_4 is selected from the group consisting of H, OH,

R_5 is selected from the group consisting of H, CH_2OH and a monovalent radical containing from 5 to 20 carbon atoms and from 1 to 8 nitrogen atoms; the radical can further comprise other functional groups such as carboxyl and hydroxyl.

v)



wherein

each Y is independently selected from the group consisting of C and N,

R_6 is selected from the group consisting of cyclopropyl, phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-fluoroethyl and ethyl;

R_7 is selected from the group consisting of H, amino, methyl,

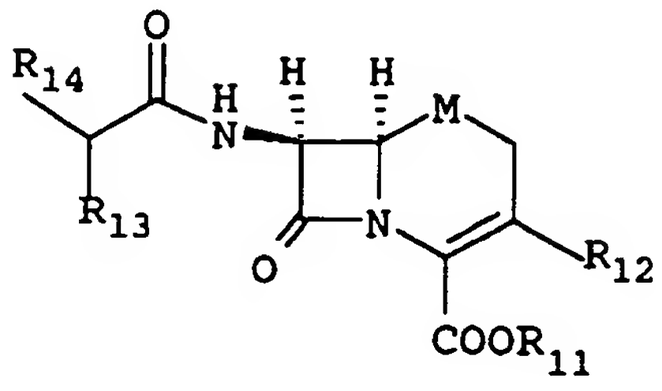
R_8 is selected from the group consisting of H and F;

R_9 is selected from the group consisting of H, methyl and a monovalent radical containing from 1 to 20 carbon atoms and from 1 to 4 nitrogen atoms;

R_{10} is selected from the group consisting of H, Cl and F;

R_6 e R_{10} can unite to form an optionally substituted six membered ring optionally containing up to two heteroatoms selected from the group consisting of oxygen and sulfur:

vi):



wherein

M is selected from the group consisting of sulfur, carbon or oxygen;

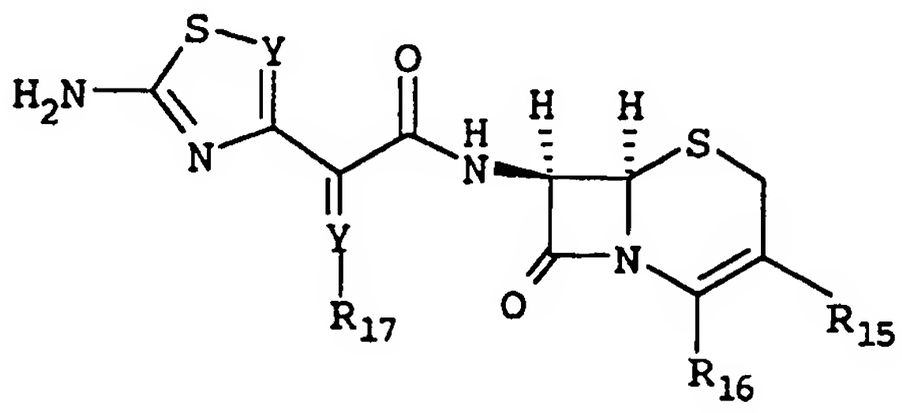
R_{11} is selected from the group consisting of H, pivaloyloxymethyl,

R_{12} is selected from the group consisting of chlorine and a monovalent radical containing from 1 to 5 carbon atoms, from 0 to 5 nitrogen atoms and from 0 to 1 sulfur atoms;

R_{13} is selected from the group consisting of amino, hydroxyl and monovalent radical containing from 1 to 10 carbon atoms, from 0 to 5 oxygen atoms and from 0 to 5 nitrogen atoms;preferably it is selected from the group consisting of amino, hydroxyl, carboxyl and

R_{14} is an unsaturated C_6 ring, optionally substituted;

vii)



wherein:

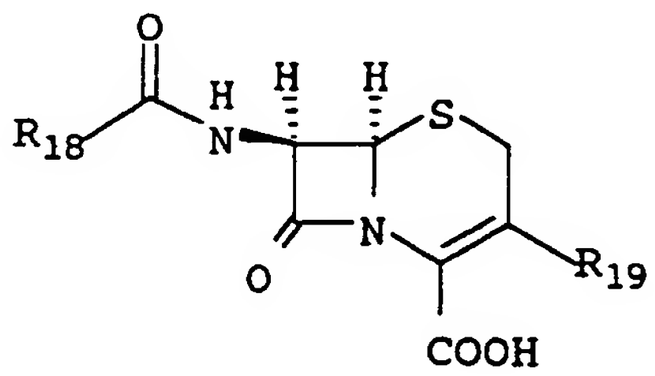
each **Y** is independently selected from the group consisting of carbon and nitrogen

R_{15} is selected from the group consisting of hydrogen and a monovalent radical containing from 1 to 12 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms;

R_{16} is a monovalent radical containing from 1 to 10 carbon atoms and from 2 to 8 oxygen atoms; preferably it is selected from the group consisting of carboxyl, $(CH_3)_3CCOOCH_2OCO$- and $(CH_3)_2CHOCOOCH(CH_3)OCO$-; when R_{15} is a quaternary ammonium cation, R_{16} is optionally a $-COO^-$;

R_{17} is selected from the group consisting of -OH and a monovalent radical containing from 1 to 12 carbon atoms and from 0 to 4 oxygen atoms, preferably it is selected from the group consisting of -OH, $-OCH_3$, $-CH_2CH_3$, $-OCH_2COOH$, $-CH_2COOH$, $OC(CH_2)_3$-COOH.

viii)

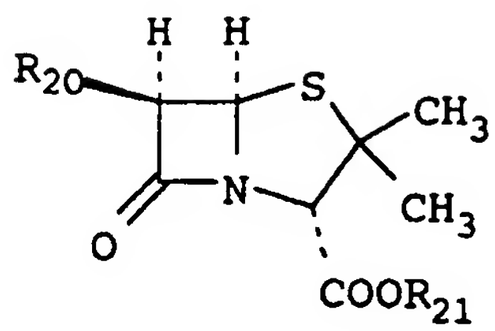


wherein:

R_{18} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

R_{19} is selected from the group consisting of H and a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 6 nitrogen atoms and from 0 to 3 sulfur atoms;

ix)

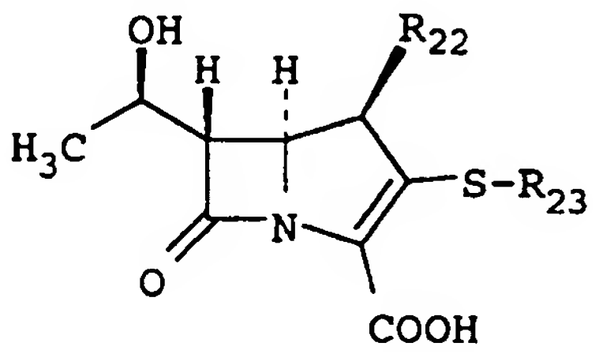


wherein:

R_{20} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms, from 0 to 3 fluorine atoms and from 0 to 3 chlorine atoms;

R_{21} is selected from the group consisting of H and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms;

x)

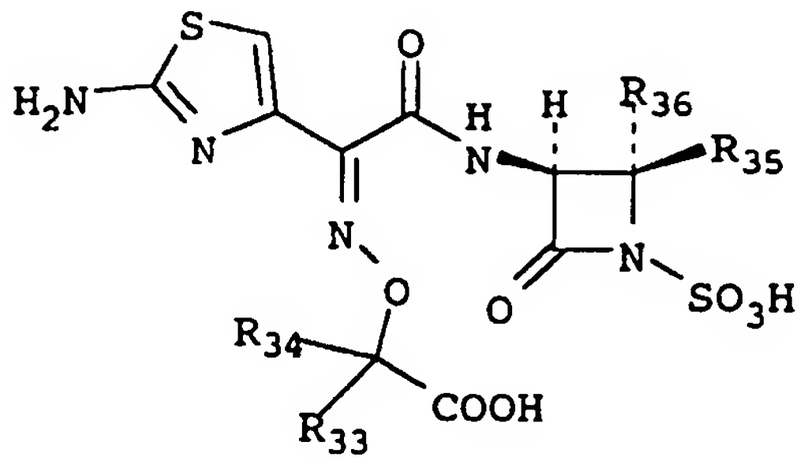


wherein:

R_{22} is selected from the group consisting of H and methyl;

R_{23} a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms and from 1 to 5 nitrogen atoms;

xi)

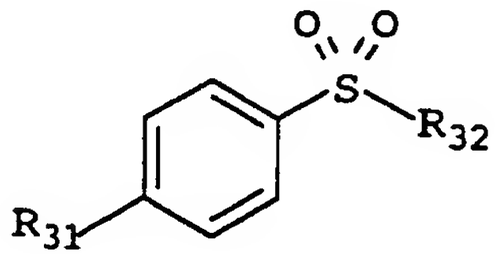


wherein:

R_{33} , R_{34} and R_{36} are independently selected from the group consisting of H and CH_3;

R_{35} is selected from the group consisting of H and $-CH_2OCONH_2$,

xii)

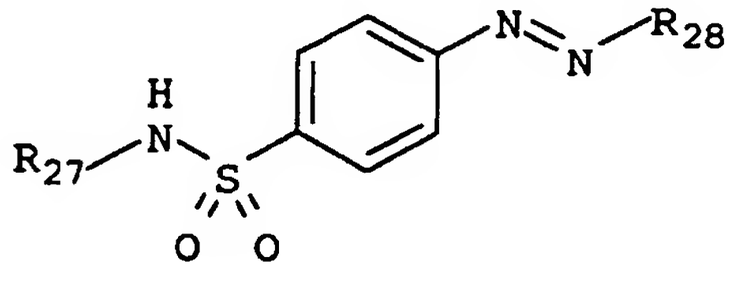


wherein:

R_{31} is selected from the group consisting of $-NH_2$, $-CH_2NH_2$ and $-NHCH_2Ph$

R_{32} is selected from the group consisting of $-NH_2$, $-NHR_{26}$ and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 5 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; wherein R_{26} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

xiii)

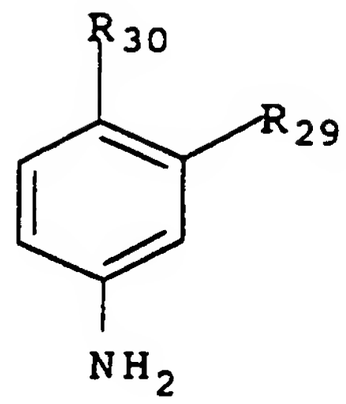


wherein:

R_{27} is selected from the group consisting of H and 4,6-dimethyl-2-pyrimidinyl;

R_{28} is a phenyl group substituted in at least 2 of the positions 2, 3, 4 and 6 by a group selected from hydroxyl, carboxyl and amino;

xiv)

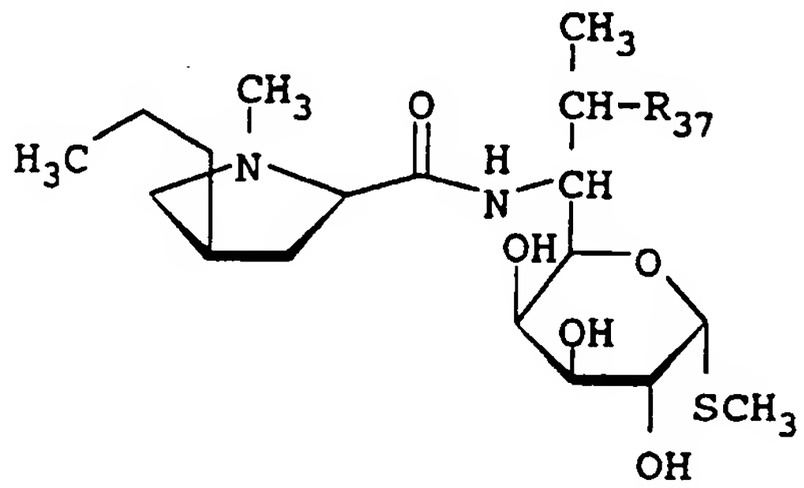


wherein:

R_{29} is selected from the group consisting of hydrogen and hydroxyl

R_{30} is selected from the group consisting of carboxyl, phenoxycarbonyl, 4-(amino)phenylsulfinyl, hydrazinocarbonyl;

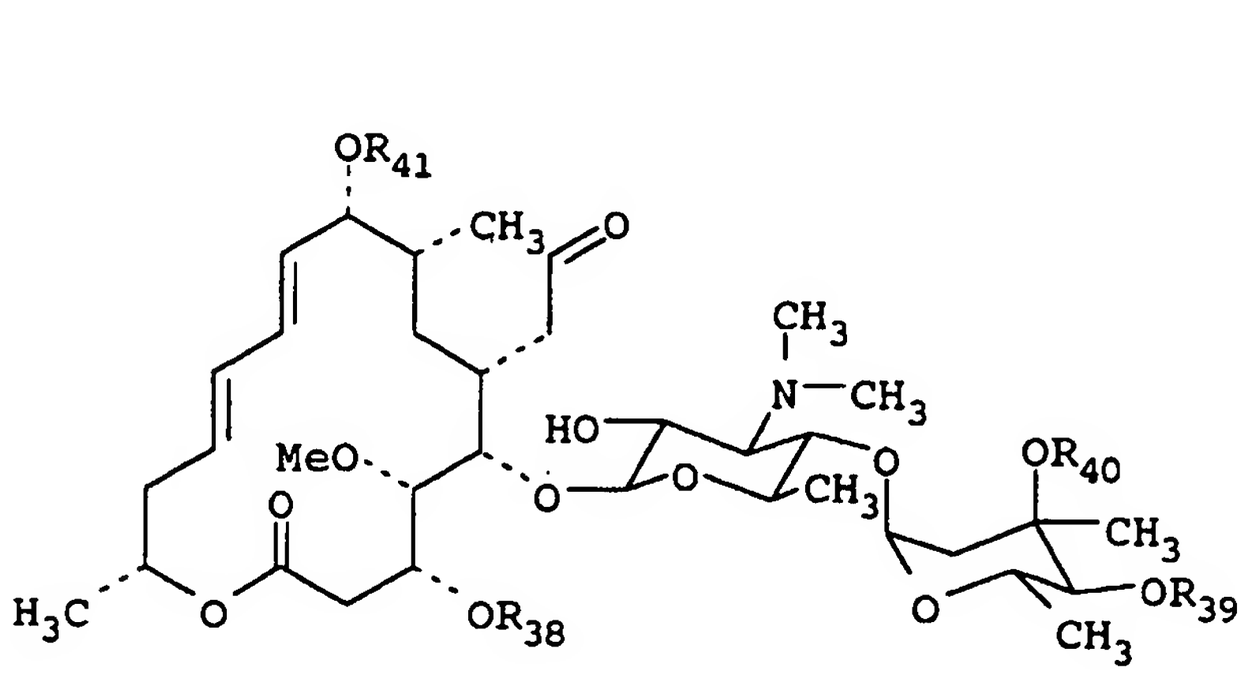
xv)



wherein:

R_{37} is selected from the group consisting of Cl and -OH;

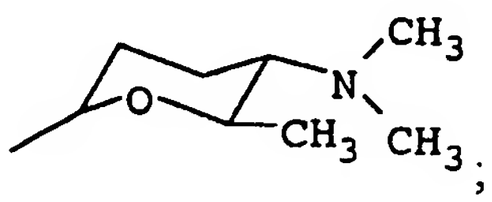
xvi)



wherein:

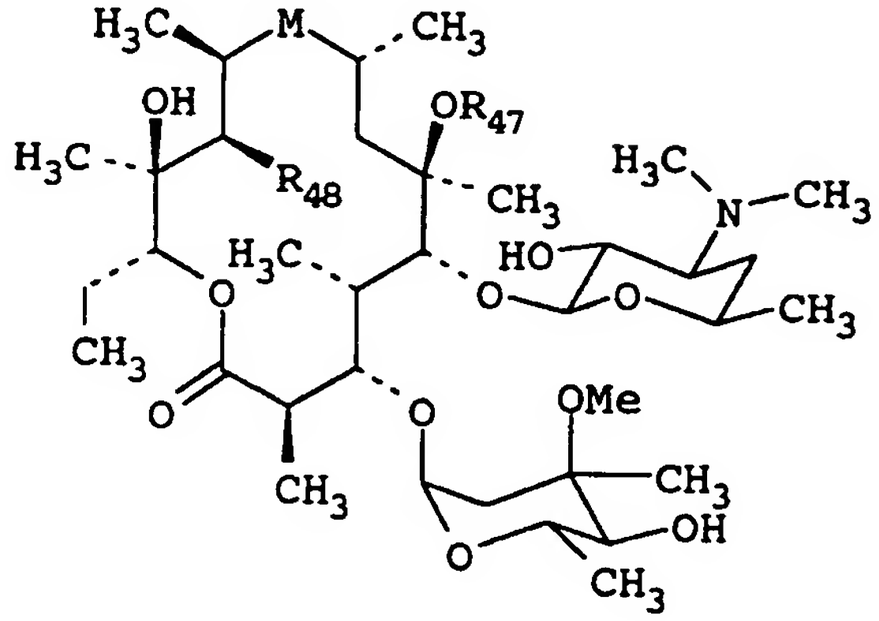
R_{38} R_{39} R_{40} are independently selected from the group consisting of H and acyl; preferably they are selected from the group consisting of H, acetyl, propionyl, butyrryl, valeryl

R_{41} is independently selected from the group consisting of H and



;

xvii)

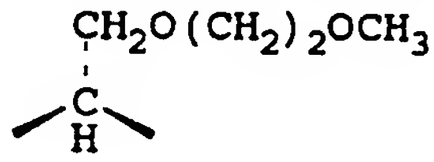


wherein:

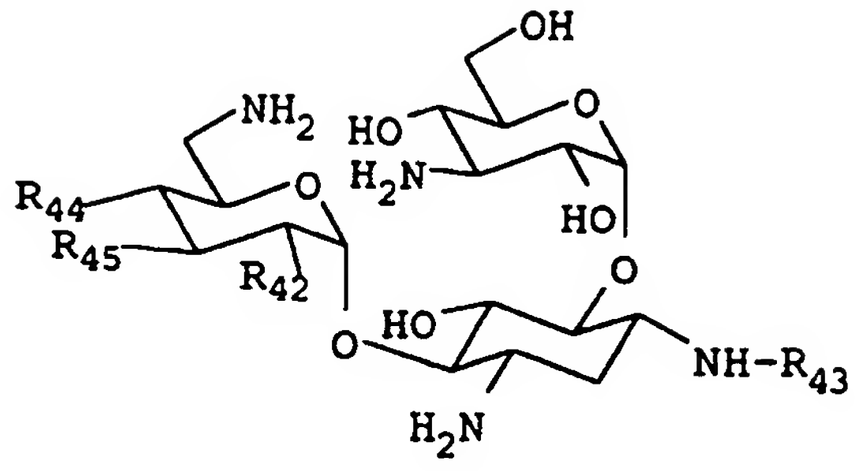
R_{47} is selected from the group consisting of H and $-CH_3$

M is selected from the group consisting of CO, N-methyl-aminomethylene and $-CH(NHR_{49})-$ wherein R_{49} is a substituted methylene bridge connecting N with R_{48}

R_{48} is hydroxyl or, when M is $-CH(NHR_{49})-$, is -O-;

Preferably R_{49} is  ;

xvii)



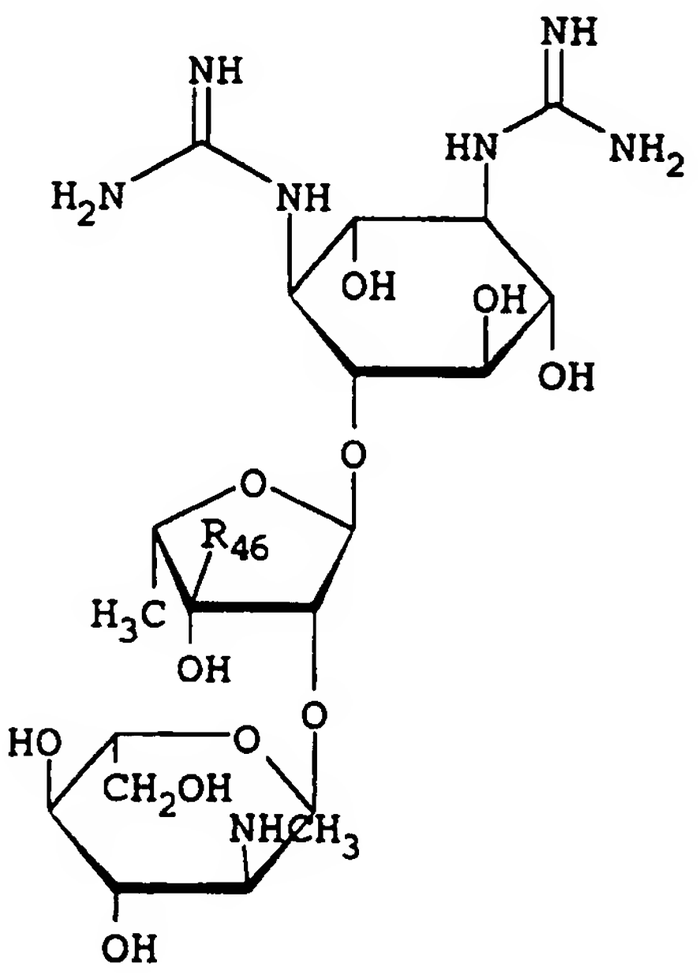
wherein:

R_{42} is selected from the group consisting of hydroxyl and amino;

R_{43} is selected from the group consisting of hydrogen, (R) and (S)-4-amino-2-hydroxybutyrryl

R_{44} and R_{45} are independently selected from the group consisting of hydrogen and hydroxyl.

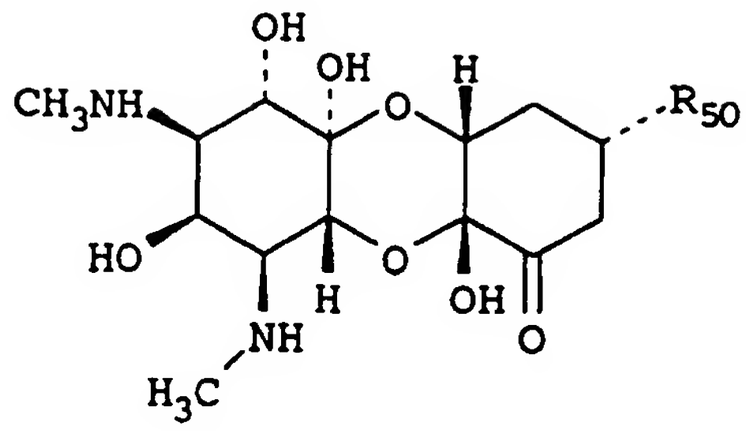
xviii)



wherein:

R_{46} is selected from the group consisting of $-CH_2OH$ and $-CHO$;

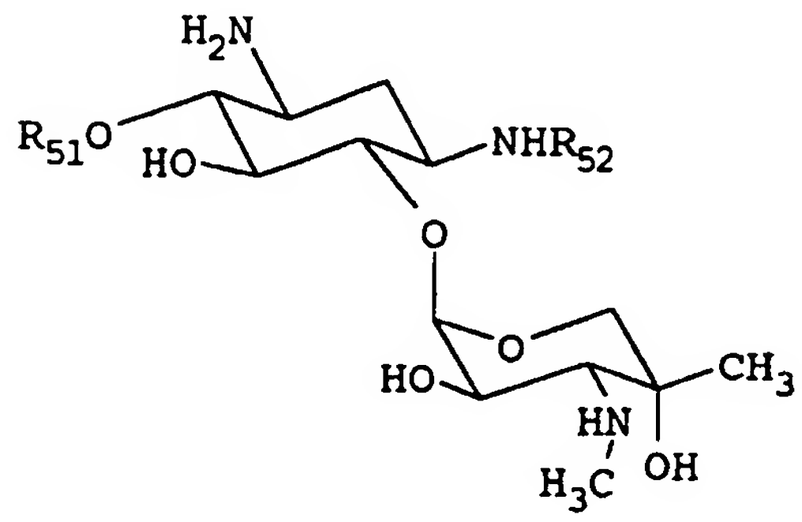
xix)



wherein:

R_{50} is a C_1-C_4 alkyl, preferably it is selected from the group consisting of methyl and n-butyl.

xx)

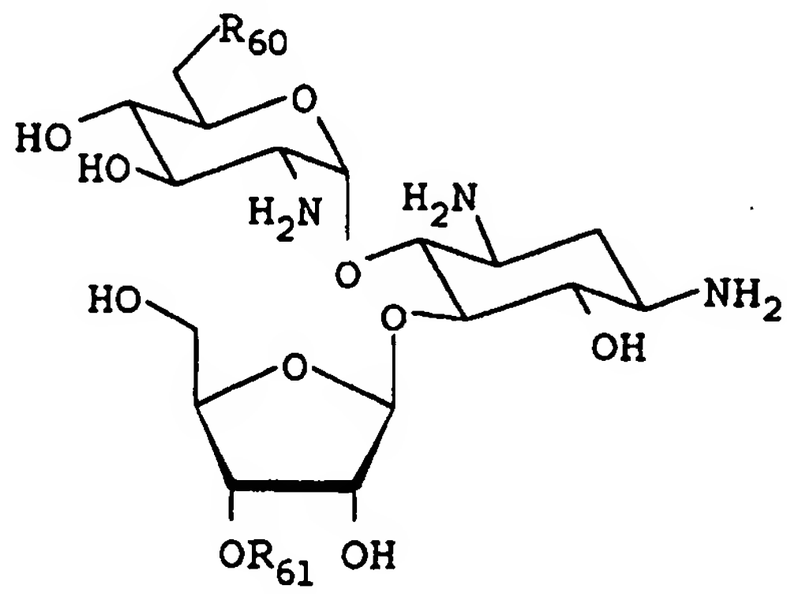


wherein:

R_{51} is independently selected from the group consisting of 3-amino-6-(aminomethyl)-3,4-dihydro-2H-pyran-2-yl and 2-amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-eritro-hexopyranosyl,

R_{52} is selected from the group consisting of H and $-CH_2CH_3$.

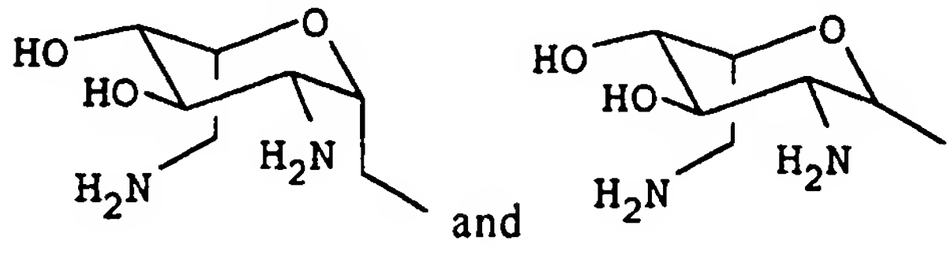
xxi)



wherein:

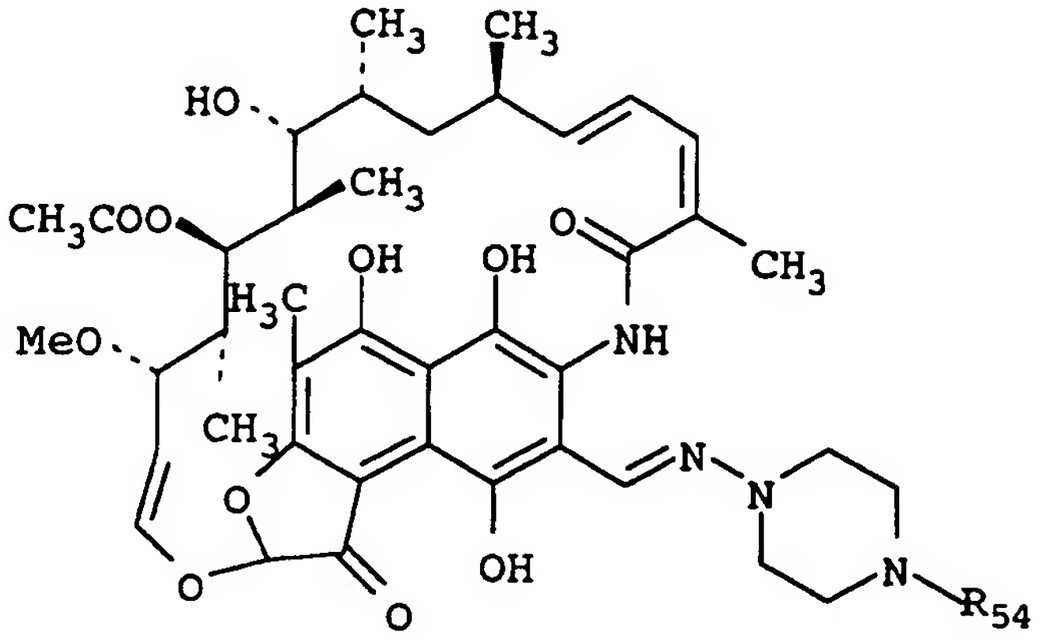
R_{60} is selected from the group consisting of –OH and $–NH_2$;

R_{61} is selected from the group consisting of H,



and

xxii)



wherein R_{54} is a C_1-C_4 linear or cyclic alkyl, preferably it is selected from the group consisting of methyl and cyclopropyl.

10. Composition according to claim 8 wherein the drug is selected from the group consisting of: Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, Paracetamol, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Ketorolac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Tenoxicam, Piroxicam, Meloxicam, Tenidap, Aceclofenac, Acemetacin, 5-amino-acetylsalicylic acid, Alclofenac, Alminoprofen, Amfenac, Bendazac, α-bisabolol, Bromosaligenin, Bucloxic acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Diflunisal, Ditazol, Enfenamic acid, Etofenamate, Felbinac, Fenclozic acid, Fendosal, Fentiazac, Fepradinol, Flufenamic acid, Flunixin, Flunoxaprofen, Flurbiprofen, Glucametacin, Glycol salicilate, Ibuproxam, Isofezolac, Isoxepac, Isoxicam, Lornoxicam, Meclofenamic acid, Mefenamic acid, Metiazinic acid, Niflunic acid, Oxaceprol, Oxaprozin, Oxyphenbutazone, Parsalmide, Perisoxal, Olsalazine, Pirprofen, Protizinic acid, Salacetamide, Salicilamide O-acetic acid, Salsalate, Suxibuzone,

Tiaramide, Tinoridine, Tolfenamic acid, Tropesin, Xenbucin, Ximoprofen, Zomepirac, Tomoxiprol.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/15340

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 21193 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 May 1998 (1998-05-22) cited in the application claims	1-10
X	WO 95 29172 A (GECZY JOSEPH ;THERABEL RESEARCH SA (BE); CYCLOLAB KFT (HU); SZEJTL) 2 November 1995 (1995-11-02) cited in the application claims	1-10
Y	WO 00 61537 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application claims	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2002	11/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Berte, M

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/EP 01/15340

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application claims	1-10
Y	WO 00 61604 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application claims	1-10
E	WO 01 00563 A (NICOX SA ;ANTOGNAZZA PATRIZIA (IT); BENEDINI FRANCESCA (IT)) 4 January 2001 (2001-01-04) claims 1,6	1-10
Y	WO 94 12463 A (HCT HEALTH CARE TRADING LTD ;ARENA BARBARA (IT)) 9 June 1994 (1994-06-09) cited in the application claims	1-10
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Y	WO 97 31654 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 4 September 1997 (1997-09-04) claims	1-10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-10 relate to an extremely large number of possible compounds. In fact, the claims contain so many variables or possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the examples and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/15340

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International Application No
PCT/EP 01/15340

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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Information on patent family members

Ig stional Application No
PCT/EP 01/15340

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(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
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(22) International Filing Date:
18 December 2001 (18.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2000A002803
22 December 2000 (22.12.2000) IT

(71) Applicant *(for all designated States except US)*: **NICOX S.A.** [FR/FR]; 2455, route des Dolines, Espace Gaia II - Bâtiment I, F-06906 Sophia Antipolis Cedex (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TRESPIDI, Laura** [IT/IT]; Via Lungo Adda, 56, I-26026 Pizzighettone (IT). **DEL SOLDATO, Piero** [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

(74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi S.p.A., Corso dei Porta Vittoria, 9, I-20122 Milano (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/051385 A1

(54) Title: SOLID DISPERSIONS OF NITRATE ACTIVE PRINCIPLES

(57) Abstract: The invention relates to solid dispersions of nitrate active principles in at least one polymer chosen from the group consisting of polyvinyl pyrrolidone, cellulose derivatives or polyethylene glycol, their production processes and pharmaceutical formulations including said dispersions.

Solid dispersions of nitrate active principles

FIELD OF THE INVENTION

The present invention relates to solid dispersions of nitrate active principles characterized by an increased dissolution rate and/or apparent solubility of said active principles and to a method for their production.

STATE OF THE ART

The applicant has developed a number of active principles, characterized by the presence in their structure of a nitro group, having remarkably advantageous pharmacological properties. These active principles are described in the patents: EP670825, EP722434, EP759899, EP609415, US5703073, and in the patent applications WO98/15568, WO98/21193, WO00/51988, WO00/61537, WO00/61541, WO00/61604, WO00/25776, MI99A001817.

Unfortunately, the utility of many of the above mentioned active ingredients is limited by their scarce solubility in water, which results in an insufficient and irregular absorption and a slow onset of the pharmacological action. This last aspect is particularly problematic in case of active ingredients such as, for instance, antinflammatory active ingredients and/or analgesics for which a rapid onset of the therapeutic action is of fundamental importance.

Thus, there is as need to develop new pharmaceutical formulations for the administration of nitrate active principles which, compared with traditional formulations, are characterized by an improved bioavailability and a faster onset of action.

It is known that the dissolution rate of poor water-soluble drugs can be increased by their conversion to the corresponding amorphous forms. A technique which can be used to this purpose is the formation of a solid dispersion of the active agent in an inert matrix, usually of polymeric nature. Nevertheless, this technique does not always allow to obtain the amorphous form and consequently the increase in dissolution rate of the active agent. Several parameters such as, for instance the interactions between the polymer and the active ingredient, the ratio between then and the production technique adopted influence the chemical-physical features of the solid dispersion obtained. Thus, for each particular active ingredient it is necessary to select both the polymer and the operative conditions for the preparation of the dispersion that lead to the conversion to the amorphous form.

SUMMARY OF THE INVENTION

The inventors have now found that it is possible to obtain an increase in the dissolution rate and/or the apparent solubility and consequently in the bioavailability of nitrate active principles by forming solid dispersions of said active principles characterized in that the inert matrix includes at least one polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

Therefore, the present invention refers to solid dispersions comprising at least one nitrate active principle and a hydrophilic polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

DESCRIPTION OF THE FIGURES

Figures 1, 2 and 3 show the thermograms of the crystalline form and of the amorphous solid dispersion according to the present invention of the following derivatives:

4- acetylaminophenyl ester of 4 nitroxybutanoic acid (NCX701)

2- (acetyloxy-benzoic-acid-3-nitroxymethyl) phenyl ester (NCX 4016)

(hydroxycortisone 21-[(4'nitroxymethyl)benzoate] (NCX 1022)

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to solid dispersions comprising at least one nitrate active ingredient and a hydrophilic polymer chosen among polyvinyl pyrrolidone, preferably having a molecular weight comprised between that of the polyvinyl pyrrolidone K17 and that of polyvinilpyrrolidone K30, cellulose ethers and polyethylene glycol, preferably having a molecular weight higher than that of PEG 1000, and more preferably PEG with a molecular weight higher than that of PEG 1500 and lower than that of PEG 6000. Among the cellulose ethers particularly preferred is the hydroxypropylmethylcellulose, preferably having a viscosity at 20°C, in a 2% aqueous solution, lower than 50 cPs, and preferably hydroxypropylmethylcellulose with viscosity comprised between 5 and 50 cPs.

By "nitrate active principles" it is meant compounds having formula (I).

$$A\text{-}X_1\text{-}L\text{-}(W)_p\text{-}NO_q \qquad (I)$$

wherein:

p is an integer equal to 1 or 0;

q is an integer equal to 1 or 2;

A=R-T_1-, wherein **R** is the radical of a pro-drug having formula **R-T_1-Z**, chosen among the therapeutic classes of drugs reported here after, wherein

Z is **H, OH, NH_2, NHR_3, $N(R_3)_2$**, wherein R_3 is a linear or branched C_1-C_5 alkyl radical

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = an oxygen atom, a sulphur atom or NR_2 wherein R_2 is hydrogen or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integer and equal to zero or 1, provided that t = 1 when t' = 0; t = 0 when t' = 1;

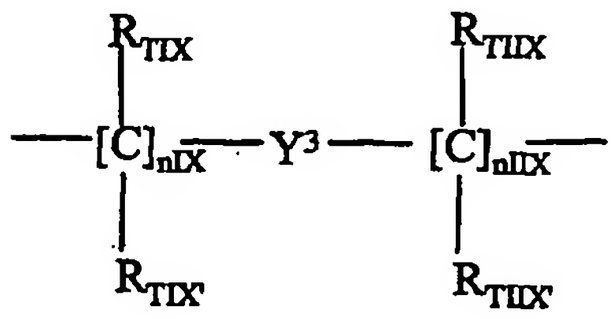
X_1 = $-T_B-Y-T_{BI}$ wherein T_B and T_{BI} are the same or different

T_B = (CO) when t = 0, T_B = X when t' = 0, being X as above defined;

T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$ wherein tx and txx are 0 or 1; with the proviso that tx = 1 when txx = 0; tx = 0 when txx = 1; X is as above defined;

Y is a bivalent bridging group chosen among the following:

1)



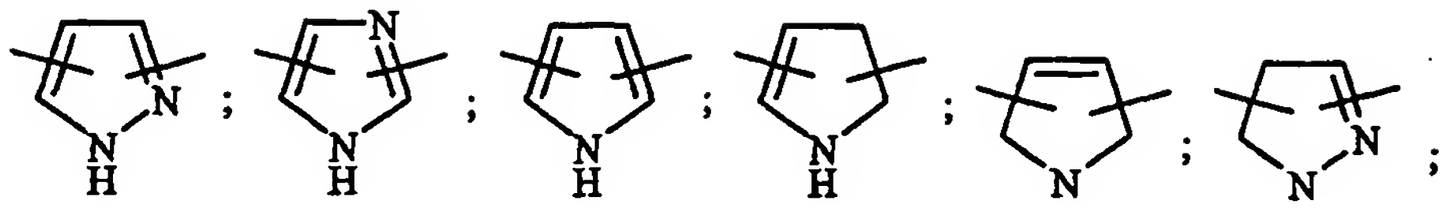
wherein:

nIX is an integer comprised between 0 and 3, preferably 1;

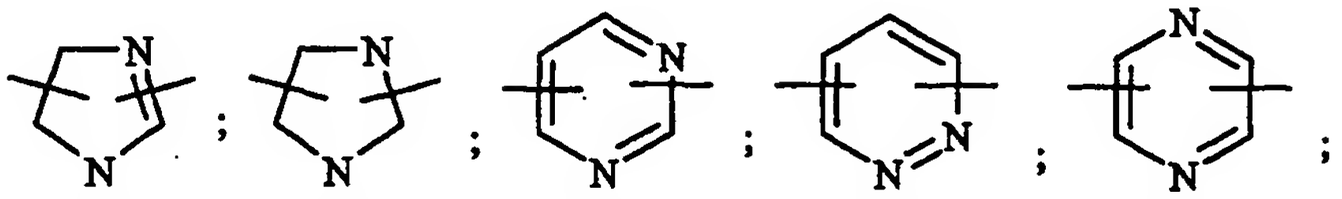
nIIX is an integer comprised between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal or different from one another, are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

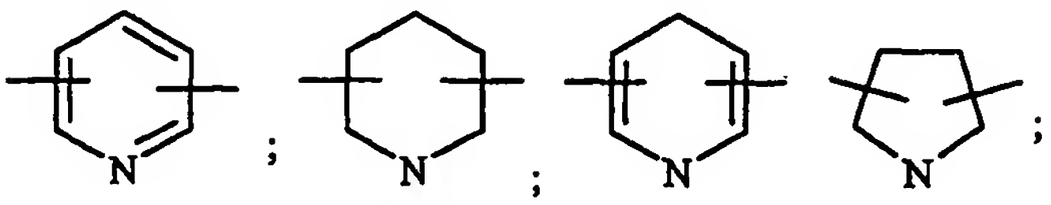
Y^3 is a saturated , unsaturated or aromatic heterocyclic ring having 5 or 6 atoms and containing one or two nitrogen atoms, Y^3 is preferably chosen among the following bivalent radical:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



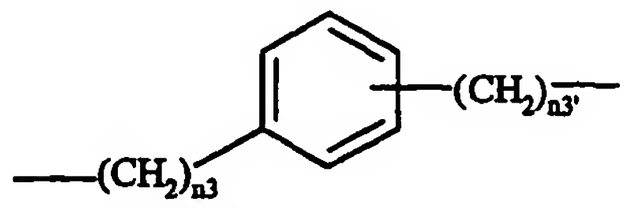
(Y12) (Y13) (Y14) (Y15)

wherein (Y12) is preferred ;

2) an alkylene group R' wherein R' is C_1-C_{20} linear or branched when possible, having preferably 2 to 6 carbon atoms, optionally substituted with at least one of the following groups: $-NH_2$, -OH or $-NHCOR_3$, wherein R_3 is a linear or branched C_{1-5} alkyl;

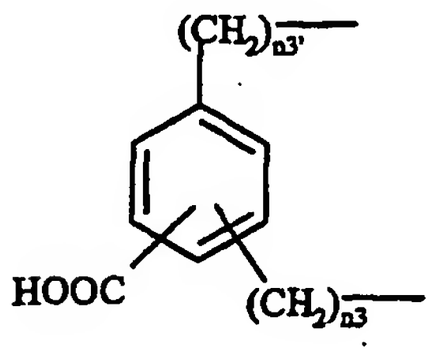
3) a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with side chains R', wherein R' is as defined above, and at least one carbon atom of the cycloalkylenic ring can be optionally substituted with etheroatoms.

4)



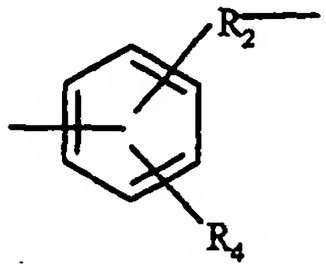
wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

5)



wherein n3 and n3' have the above indicated meaning,

6)

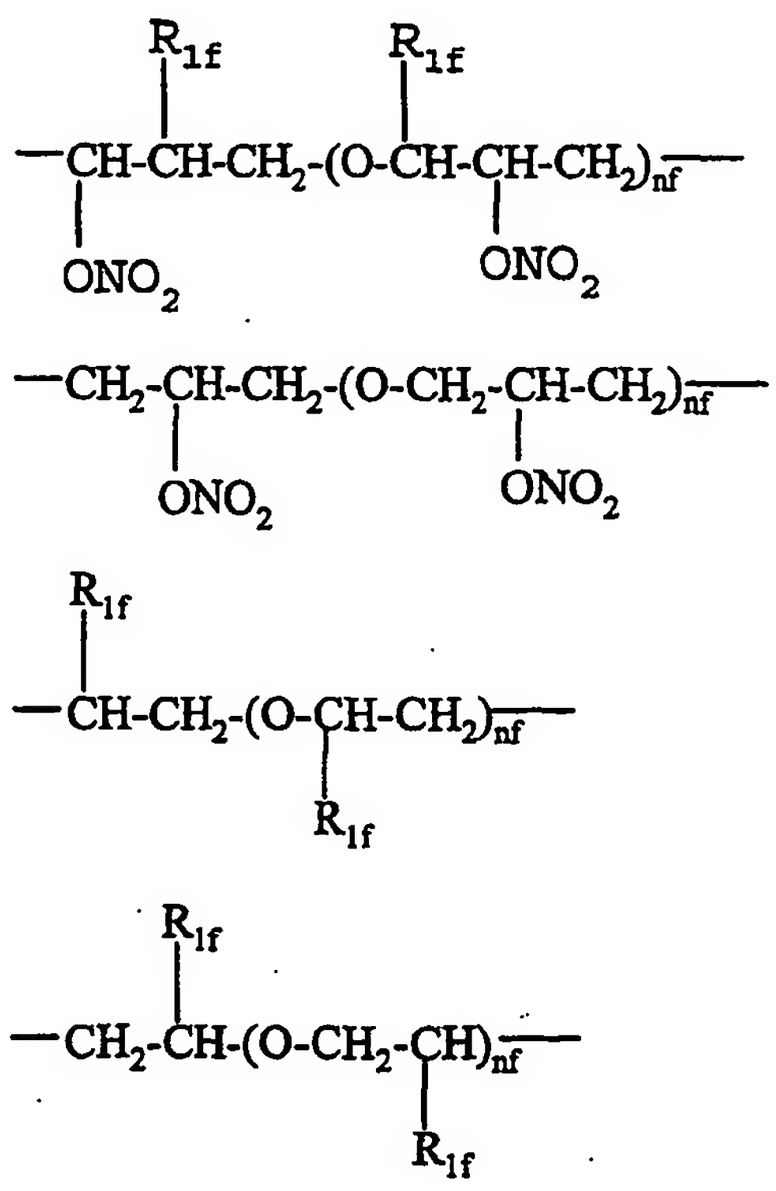


wherein

R_4 is hydroxy, hydrogen, alkoxy R_5O- wherein R_5 is a linear, branched or cyclic C_{1-10} alkyl group, preferably R_5 is a methyl group;

R_2 is a linear or branched C_2-C_{10} alkenyl group, including at least one double bond, preferably R_2 is the ethenylene group (-CH=CH-);

7)



wherein R_{1f} = H, CH_3 and nf is an integer from 0 to 6; preferably from1 to 4;

8) or Y is the bivalent radical whose precursor Z-T_B-Y-T_{BI}-Z, wherein Z is as defined above and it is chosen among the following compounds:

aspartic acid, histidine, 5-hydroxytryptophan, 2-thiouracil, 2-mercaptoethanol, hesperidine, secalcipherol, 1-α-OH-Vitamin D2, flocalcitriol, 22-oxacalcitriol, 24,28-

methylen-1α-hydroxyvitamin D2, succinic acid, L-carnosine, anserine, sel nocysteine, selenomethionine, penicillamine, N-acetylpenicillamin , cystein , N-acetylcysteine, glutathione, gallic acid, ferulic acid, gentisic acid, citric acid, caffeic acid, hydrocaffeic acid, p-coumaric acid, vanillic acid, chlorogenic acid, kynureic acid, siringic acid, nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfuretin, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydrohydroxyquinone, propyl gallate, saccharose, 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate, allopurinol, conyferyl alcohol, 4-hydroxyphenethyl alcohol, p-coumaric alcohol, curcumin, N,N'-diphenyl-p-phenylenediamine, thionine, hydroxyurea, 3,3'-thiodipronic acid, fumaric acid, dihydroxymaleic acid, N-methylendiethanolamine, thiodiethylenglycol, 1,4-dioxane-2,6-dimethane, tetrahydropyran-2,6-di-methanol, 4H-pyran-2,6-di-methanol, cyclohexene-1,5-dimethanol, 1,4-dithian-2,6-dimethanol, thiophene-2,5-di-methanol, oxazole-2,5-di-methanol.

L= covalent bond, or **L = X**, **X** being as defined above, **L = (CO)**

W = Y_T-X- wherein **Y_T** has the same meanings of **Y**, but is different from **Y**,

R-T_1-Z is chosen among the following drugs:

- Non steroidal anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, alclofenac, alminoprofen, amfenac, ampiroxicam, balsalazide, bendazac, bermoprofen, α-bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, diclofenac, CS-670, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lomoxicam, loxoprofen, mechlofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxifenbutazone, parsalmide, pemedolac, perisoxal, phenyl acetylsalicilate, pirazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicylamido-O-acetic acid, saliciylsulforic acid, salsalate, sulindac, suprofen, suxibuzone, tenidap, tenoxicam, thiaprofenic acid, thiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepi-

rac, tomoxiprol,

Analgesics: paracetamol, acetaminosalol, aminochlorthenoxazin, acetylsalicilic acid, 2-amino-4-picoline, acetylsalicylsalicilyc acid, anileridine, benoxaprofen, benzylmorphine, 5-bromosaliciylic acid acetate, bucetin, buprenorfine, butorfanol, capsaicin, cincofenol, ciramadol, clometacine, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimefeptanol, dipyrocetyl, eptazocine, etoxazen, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodon, hydromorone, hydroxypetidine, ibufenac, p-lactophenetide, levorfanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorfanol, normorphine, oxycodone, oxymorphon, pentazocine, fenazocine, fenocoll, fenoperidine, fenilbutazone, phenylsalicylate, phenilramidol, salicin, salicylamide, tiorphan, tramadol, diacereine, actarit;

- Steroids: chenodeoxycholic acid, ursodeoxycholic acid, alclomethasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chlorprednisone, clobetasol, clobethasone, clocortolone, cloprednol, corticosteron, cortisone, cortivazol, deflazacort, desonide, desoximethasone, dexamethasone, diflorasone, diflucortolone, difluprednate, estradiol, ethynilestradiol, fluazacort, flucloronide, flucortyn butyl, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halomethasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, mestranol, metilprednisolone, mitatrienediol, mometasone furoate, moxestrol, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisone, prednival, prednylidene, rimexolone, 21-acetoxy-pregnenolone, triamcinolone hexacetonide, triamcinolone acetonide, triamcinolone, tixocortol;
- Bronchodilatory drugs: acephilline, albuterol, bambuterol, bamiphylline, bevonium methyl sulfate, bitolterol, carbuterol, clenbuterol, clorprenaline, dioxetedrine, diphylline, ephedrine, epinephrine, eprozinol, etaphedrine, ethylnorepinephrine, etophylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetarine, isoprotenerol, mabuterol, metaprotenerol, oxitropium bro-

mide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-theobromoacetic acid, thiotropium bromide, tretoquinolol, tulobuterol, oxybutinyn, zaprinast.

- Expectorants and mucolitic agents: ambroxol, bromexine, domiodol, erdosteine, guaiacol, guaifenesine, glycerol iodurate, letosteine, mesna, sobrerol, stepronin, terpin, thiopronin;
- Anti-asthmatic, antiallergic and antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, hystamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, bromexine, formoterol;
- ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naftopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;
- β-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronetalol, propranolol, sotalolol, sulfinalolol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;
- Drugs for vascular disorders: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betaistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, heparine, dalteparin, dipiradamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, lamifiban, nadroparin, nicotinoyl alcohol, nylidrin, ozagrel, perhexiline, prenilamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinophedrine, tinzaparin, triflusal, xanthinol niacinate, fenilpropanolamine, midodrine;

Antidiabetics: acarbose, carbutamide, glibornuride glybuthiazol, miglitol, repaglinide, troglitazone, 1-buthyl-3-methanyl-urea, tolrestat, nicotinamide;

Antitumoral drugs: ancitabine, anthramicine, azacitidine, azaserine, 6-azauridi-

ne, bicalutamide, carubicine, carzinophilin, chlorambucil, chlorozotocin, citarabine, daunorubicine, defosfamide, demecolcine, denopterine, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicine, droloxifene, edatrexate, eflornithine, enocitabine, epirubicine, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracyl, gemcitabine, hexestrol, idarubicine, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, micophenolic acid, ninopterine, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamicine, podofillic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, tiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicine;

- Antiulcer drugs: ε-acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazol, ornoprostil, pantoprazol, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;
- Antihyperlipidemic drugs: atorvastatine, cilastatine, dermostatine, fluvastatine, lovastatine, mevastatine, nistatine, pentostatine, pepstatine, privastatine sodium salt, simvastatine;
- Antibacterial drugs: amdinocillin, amoxicillin, ampicillin, apalcillin, apicyclin, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazoline, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracicline, cinoxacine, clavulanic acid, clofoctol, clometocilline, cloxacilline, cyclacillin , cycloserine, demeclocicline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, me-

clocycline, meropenem, metampicillin, metacicline, meticillin sodium salt, mezlocillin, minocicline, moxalactam, mupirocin, myxin, negamycine, novobiocin, oxacillin, pamipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, pheneticillin potassium salt, pipaciclyne, piperacillin, pirlimycin, porfiromycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidine, argininsa, arbekacin, apramycin, amikacin, azithromycin, bacampicillin, cefcapene pivoxil, cefpodoxime proxetil dapsone, deoxydihydrostreptomycin dibekacin, etambutol, flumequine, guamecycline, nifurpirinol, nifurprazine, nitroxoline, glyconiazide, isoniazide, opiniazide, mupirocin, negamycin, netilmicyn, pipacycline, fortimycins, gentamycin, ibostamycin, lincomycin, micronomycin, midecamycin, miokamycin, oleandomycin, paromomycin, rosaramycin, sisomycin, streptomycin, tobramycin, trospectomycin, claritromycin, diritromycin, enviomycin, erithromycin, josamycin, midecamycin, miocamycin, rifabutine, rifamide, rifamycin, rifaxymine, rokitamycin, spiramycin, troleandromycin, viomycin, virginiamycin; p-aminosalicylic acid, benzilpenicillinic acid, acetil sulfametossipirazine, acediasulfone, 4-sulfanylamidosalicylic acid, 4,4'-sulfinyldianiline, 4'-(methylsulfamoyl)sulfanylanilide, 2-p-sulfanilylanilinoethanol, N-sulfanilyl-3,4-xylamide, p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, salazosulfadimidine, salinazid, succisulfone, sulfabenzamide, sulfacetamide, sulfachlorpiridazine, sulfachrysoidine, sulfacitine, sulfadiazine, sulfadicramide, sulfadimetoxine, sulfadoxine, sulfaetidol, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfametazine, sulfametizol, sulfamethomidine, sulfametoxazol, sulfametoxypiridazine, sulfamethyltiazol, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanylamide, sulfanylilurea, sulfaperine, sulfafenazol, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfatiazol, sulfathiourea, sulfisomidine, sulfisoxazol, sultamicillin, tiazosulfone, mafenide, clofazimine, carbomycin, clomocycline, meclocycline, metampicillin, meticillin, metronidazole, mezlocillin, moxalactam, oxytetracycline, piromidic acid, pivampicillin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, grepafloxacin, lomefloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, rifanpin, rufloxacin, ta-

lampicillin, trovafloxacin, tosufloxacin, sparfloxacin;

Antiviral drugs: aciclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxine, ribavirine, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

- Inhibitors of bone reabsorption: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;
- Drugs for dementia: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

When the compounds include at least one asymmetric carbon atom, the products can be used in racemic mixture or in form of single enantiomer.

The active principle in the solid dispersions of the invention is in amorphous form. By "amorphous form" of a compound it is meant a solid form of that compound that when subjected to DSC analysis does not show the melting endothermic peak.

When the active principle is in the solid dispersions of the present invention it is characterized by a higher dissolution rate and therefore a higher bioavailability than in the non dispersed form. As it will be shown in detail in the following examples, a particularly high increase in the dissolution rate occurs when the hydrophilic polymer used in the dispersion is polyvinylpyrrolidone. Thus, the use of the polyvinylpyrrolidone as the hydrophilic polymer is particularly preferred when a very fast release of the active agent is desired.

Preferably the solid dispersions of the present invention comprise one or more nitrate active principles in amounts comprised between 5% and 60% w/w and preferably between 15% and 40% w/w and the hydrophilic polymer in amount ranging from 50% to 90%, preferably between 70% and 85% w/w.

Optionally, the solid dispersions of the present invention comprise also pharmaceutically acceptable excipients such as, for instance, wetting and solubilising agents in amount preferably ranging from 2% to 20%. Preferably the solubilising agents are surfactants, and among them most preferred are polysorbat s, sters and ethers of polyethylen glycols, polihydroxylated castor oil and sodium laurylsul-

phate. The solid dispersion of the invention can be produced by using process s known in the art such as, for instance, the methods bas d on co-precipitation, the methods based on melting, which consist in melting together the active agent and the carrier and then cooling the melted mass, among them it is mentioned in particular "snap-cooling" where the cooling of the melted mass is carried out on stainless steel plates, "injection molding" where the molten mass is injected into a mould, hot melt extrusion where the active principles and the carrier mixture while flowing through the extruder is contemporaneously melted, homogenized and then extruded in the form of pellets, granules and other intermediates to be used for the production of tablets (the advantage of this technique is that the mixture is subjected to high temperatures just for one minute and it is therefore suitable for active agents sensible to high temperatures), "spray congealing", where cooling of the melted mass is carried out by freezing, and the methods based on solvent evaporation, consisting in dissolving the active agent and the carrier in the same solvent, or in forming an emulsion of the active agent and of the carrier in the solvent. Among these methods a technique allowing to easily and quickly obtain solid dispersions is "spray drying". An especially preferred process for the production of the solid dispersions of the invention is a spray-drying process comprising the following steps:

a) dissolving the active principle in a solution or suspension of the hydrophilic polymer;

b) spraying the mixture obtained in step (a) through the standard nozzle of a sprayer at a flow rate ranging from 5 to 60 ml/min and at a temperature of the inlet air comprised between 50°C and 130°C.

The solution or suspension of step a) can be realized in solvents such as, for instance, water, ethanol, isopropyl alcohol, methylen chloride, butanol, cyclohexane, hexane, acetone or mixture thereof. The choice of the solvent depends on the characteristics of solubility of the active agent which has to be dissolved.

The concentration of polyvinyl pyrrolidone, hydroxypropylmethylcellulose or polyethylene glycol in said solution or suspension is comprised between 1% and 10% w/v and preferably between 2.5% and 7.5% w/v.

The active principle ingredient is added to said solution or suspension in such an

amount to obtain a concentration comprised between 0.1% and 10% w/v and preferably between 0.5% and 7.5% w/v.

Optionally, at least one of the above mentioned pharmaceutically acceptable excipients can be added to the solution or suspension in such an amount as to obtain a concentration of said excipients comprised between 0.01% and 10% w/v and preferably between 0.05% and 5% w/v.

The spraying carried out in step b) is preferably carried out at a flow rate comprised between 5 and 60 ml/min and at an inlet air temperature comprised between 50°C and 130°C.

The solid dispersions of the present invention can be administrated as such, in form of powder, or used, for instance, for the production of granulates, tablets, capsules, suspensions, solutions, suppositories and aerosols.

Therefore, a further object of the present invention are pharmaceutical formulations for oral, parenteral, rectal, (trans)dermic or (trans)mucosal administration of the nitrate active principles comprising the solid dispersions of the invention.

If compared to conventional formulations, the formulations of the invention allow to improve the bioavailability and the onset of action of the nitrate active principles.

The invention will be now explained in detail by the following examples to be considered as a not limiting explanations of the invention.

EXAMPLE 1

Preparation of solid dispersions of the 4- acetylaminophenyl ester of the 4-nitroxybutanoic acid (NCX701).

A solution in methylene chloride/ethanol (90/10 v/v) including 0.8823% w/v of 4-acetylaminophenyl ester of the 4-nitroxybutanoic acid and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. This has then been sprayed through the standard nozzle (inner diameter 1 mm) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) at a flow rate of 20 ml/min while keeping an inlet hot air temperature of 60°C.

The obtained product has then been analysed by scanning calorimetry using a DSC T.A.2910 of T.A. INSTRUMENTS, with a heating interval and scanning rate of 10°C/min. under constant nitrogen flow. The obtained thermogram, reported in Figure 1, shows that the analysed product is amorphous. In fact no thermic event

is detected in the considered temperature interval and in particular in correspondance with the melting temperature of the 4-acetylaminophenyl ester of the 4 nitroxybutanoic acid, at 78°C.

EXAMPLE 2

Evaluation of the dissolution rate of 4-acetylaminophenyl ester of 4 nitroxybutanoic acid in solid dispersion

The dissolution rate of the active principle of the solid dispersion produced in Example 1 has been evaluated, in comparison with the dissolution rate of the pure active principle in micronized form with the paddle method, described in F.U.X., using the following conditions:

dissolution means: distilled water

temperature: 37°C±0.5

stirring rate: 100 r.p.m.

The quantity of active ingredient released has been evaluated by UV spectrophotometry at a wavelength of 240 nm. The following table shows the average of the results obtained from three determinations, expressed as percentage of active principle dissolved at different time intervals:

TIME (minutes)	Micronized active principle	Solid dispersion
5	17.8	100
10	38.8	100
15	52.1	100
20	60.7	100
25	67.5	100
30	72.4	100
35	76.4	100
40	79.7	100
45	82.6	100
50	85.2	100
55	87.3	100
60	94.9	100

As it can be observed from the table, while the active principle as such is characterized by a slow dissolution in water, when this is in the form of a solid dispersion in polyvinyl pyrrolidone its dissolution is immediate, occurring in less than five minutes.

EXAMPLE 3

Preparation of solid dispersions of 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid (NCX4016)

Two solutions in methylene chloride/ethanol (90/10 v/v) having the following compositions have been prepared:

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of polyvinyl pyrrolidone K25;

2.1 % w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/p of polyvinyl pyrrolidone K25;

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of hydroxypropylmethylcellulose.

The solutions have then been sprayed as described in Example 1. The product obtained has been analysed by scanning calorimetry using a device described in the preceding example. The thermogram obtained, reported in Figure 2, shows that the analysed product is amorphous. In fact no thermic event is detected in the considered temperature interval and in particular in correspondance with the melting temperature of the 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid, at 63.52°C.

EXAMPLE 4

Determination of the dissolution rate of NCX4016 in solid dispersion

The dissolution rate of the solid dispersion produced in the example 3 has been compared with the dissolution rate of the pure NCX4016 in micronised form using the paddle method described in F.U.X., according to the following operating conditions T = 37°C±0.5°C, stirring rate:150 rpm, dissolution means: 1% sodium lauryl sulphate solution, dissolution volume: 900 ml.

The quantity of NCX4016 released has been spectrophotometrically evaluated in continuous at a wavelength 232 nm. The following table shows the average of the results obtained from 3 determinations, expressed as percentage of active principle dissolved at different time intervals.

TIME (minutes)	NCX4016 micronized	NCX4016 Solid dispersion 1	NCX4016 Solid dispersion 2	NCX4016 Solid dispersion 3
5	17.9	98.2	98.1	27.3
10	39.2	99.9	99.2	65.7
15	53.5	100	100	81.1
20	60.7	100	100	90.2
25	71.4	100	100	92.4
30	77	100	100	94.1
35	80.9	100	100	94.7
40	84.4	100	100	94.9
45	87	100	100	95.4
50	88.9	100	100	95.4
55	90.6	100	100	95.4
60	91.4	100	100	95.4

Also in this case, as it can be observed from the table, the dissolution rate of the active principle in all the three solid dispersions is higher than that of the active principle in pure form. Moreover, when the active principle is dispersed in polyvinyl pyrrolidone, the increase in the dissolution rate is remarkably high and an almost immediate release is observed.

EXAMPLE 5

Evaluation of the dissolution rate of 3-(nitroxymethyl)phenyl ester of the 2-acetoxybenzoic acid (NCX4016) in solid dispersion under condition of supersaturation

Three samples of microspheres have been exactly weighed so as to have a con-

tent of nitroaspirine of 30 mg. This quantity corresponds to about 4 times the solubility in water of the active principle.

The dissolution rate of the active principle from the above mentioned 3 solid dispersions has been compared with the dissolution rate of the pure active principle in micronized form, with the paddle method, described in F.U.X. using the following conditions:

dissolution means: distilled water

temperature: 37°c±0.5

stirring rate: 100 r.p.m.

volume = 900 ml

The quantity of NCX 4016 released has been evaluated spectrophotometrically in continuous at a wavelength 232 nm.

The samples have been taken by means of a peristaltic pump at 5 minutes intervals and for the total time of one hour.

The following table shows the average of the results obtained from three determinations, expressed as percentage of dissolved active principle at different time intervals:

TIME (minutes)	Micronized active principle	Solid dispersion 2
5	n.r.[a]	55.1
10	n.r.[a]	54.3
15	n.r.[a]	51.8
20	n.r.[a]	48.7
25	n.r.	46.9
30	Nr.[a]	44.7
35	n.r.[a]	42.8
40	n.r.[a]	40.8
45	n.r.[a]	38.6
50	n.r.[a]	37.3
55	n.r.[a]	35.7
60	n.r.[a]	34.3

a: spectrophotometrically not detectable

The quantity of active agent NCX4016 dissolved after 5 minutes is about twice the solubility of the active ingredient in the dissolution means.

EXAMPLE 6

Preparation of solid dispersions of HCT 1026 (2-fluoro-α-methyl[1.1'biphenyl]4-acetic acid-4nitrooxy butyl ester

Two solutions in methylene chloride/ethanol (90/10 v/v) with the following compositions have been prepared:

HCT 1026 0.44% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

HCT 1026 0.88% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

The solutions have then been sprayed under the same conditions used in Example 1.

EXAMPLE 7

Evaluation of the dissolution rate of the HTC1026 in solid dispersion

The dissolution rate of the HCT 1026 from the solid dispersion 1 has been evaluated, in comparison with the dissolution rate of the pure active ingredient, with the paddle method described in F.U.X. In detail, 50 mg of the solid dispersion 1 and 7.5 mg of pure active ingredient are placed in a thermostatic container at 37°C±0.5°C in 900 ml of distilled water including 1% w/v of SDS and kept under stirring at 150 rpm. The quantity of HCT 1026 passed into the solution is continuously spectrophotometrically determined in continuous at a wavelength of 245 nm.

In the following table the average of the results obtained from three determinations is reported, expressed as percentage of active principle dissolved at different time intervals:

TIME (minutes)	Pure HCT 1026	Solid dispersion 1
5	5.84	81.04
10	16.74	84.74
15	23.6	85.2
20	29.84	86.13
25	32.78	85.67
30	37.92	85.85
35	42.57	86.31
40	47.46	86.68
45	54.94	86.78
50	58.98	86.78
55	58.98	87.42
60	64.72	87.79

The results obtained show also in this case that when the active agent is in solid dispersion in polyvinyl pyrrolidone its dissolution speed is much higher than the one of the active agent in non dispersed form, and the release of more than 80% of the active principle is observed in less than 5 minutes.

EXAMPLE 8

Preparation of solid dispersions of NCX 1022 (hydroxycortisone 21-[(4'-nitroxymethyl)benzoate]

A solution of methylene chloride/ethanol (90/10 v/v) including 0.44% w/v of NCX 1022 and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. It has then been sprayed through the standard nozzle (1 mm inner diameter) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow rate of 20 ml/min keeping a temperature of the inlet hot air of 60°C.

The product obtained has then been analyzed through scanning calorimetry by using the device described in the preceding examples. The thermogram obtained, reported in Figure 3, shows that the analysed product is amorphous and degrades at a temperature lower than 200°C. In fact no thermic event is detected in the considered interval of temperature and in particular in correspondance with the melting temperature of the NCX 1022.

EXAMPLE 9

Determination of the dissolution speed of the solid dispersion of NCX 1022

The dissolution rate of the active ingredient from the solid dispersion produced in Example 6 has been compared with the dissolution rate of the pure active ingredient, using the paddle method described in F.U.X. In detail, 40 mg of the solid dispersion or 5 mg of pure NCX 1022 have been placed in a thermostated container at 37°C±0.5°C in 500 ml of distilled water including 1% w/v of Tween 80 and kept under stirring at 100 rpm. The quantity of NCX 1022 dissolved has been spectrophotometrically determined in continuous at a wavelength of 240 nm.

The following table shows the average of the results obtained from three determinations, expressed as percentage of ingredient dissolved at different time intervals:

TIME (minutes)	Micronized active principle	Solid dispersion
5	4.05	45.56
10	3.91	49.73
15	3.86	50.36
20	3.81	49.90
25	3.91	48.84
30	3.77	47.18
35	3.91	45.60
40	3.77	43.71
45	4.09	41.93
50	4.33	40.2
55	4.23	38.82
60	4.32	37.18

The results obtained show that, even if the solubility of the pure active principle almost null, with a solubilisation of only 4.3% within one hour, when this is in form of a solid dispersion in polyvinyl pyrrolidone its dissolution rate and therefore its apparent solubility remarkably increase and it is possible to obtain the release of 50% of active ingredient in less than 15 minutes.

CLAIMS

1. Solid dispersions comprising at least one nitrate active ingredient and one hydrophilic polymer chosen among cellulose ether, polyvinyl pyrrolidone, polyethylene glycol.

2. Dispersions according to claim 1 wherein said polymer is polyvinyl pyrrolidone .

3. Dispersions according to claim 1 wherein said cellulose ether is hydroxypropylmethylcellulose and it has a molecular weight such that the viscosity at 20°C of a 2% solution in water is lower than 50 cps.

4. Dispersions according to claim 1 wherein polyvinyl pyrrolidone has an average molecular weight comprised between the molecular weight of polyvinyl pyrrolidone K17 and the molecular weight of polyvinyl pyrrolidone K30.

5. Dispersions according to claim 1 wherein polyethylene glycol has an average molecular weight higher than or equal to the molecular weight of polyethylene glycol 1000.

6. Dispersions according to claim 1 wherein said active ingredient is contained in amounts ranging from 10% to 50% w/w and said hydrophilic polymer is contained in amounts ranging from 50% to 90%.

7. Dispersions according to claim 6 wherein the amount of said active ingredient is between 15% and 40% w/w.

8. Dispersions according to claim 6 wherein the amount of said hydrophilic polymer is between 60% and 85%.

9. Dispersions according to claim 1 further comprising pharmaceutically acceptable excipients.

10. Dispersions according to claim 9 wherein said excipients are contained amounts comprised between 2% and 20%.

11. Dispersions according to claim 9 wherein said pharmaceutically acceptable excipients are chosen from the group consisting of wetting and solubilising agents.

12. Dispersions according to claim 11 wherein said solubilising agents are surfactants.

13. Dispersions according to claim 12 wherein said surfactants are chosen from the group comprising polysorbates, esters and ethers of polyethylene glycols, polyhydroxylated castor oil and sodiumlauryl sulphate.

14. Pharmaceutical formulations for oral, rectal, parenteral, transcutaneous, transmucosal administration of active principles comprising the solid dispersions according to claims 1 to 13.

5

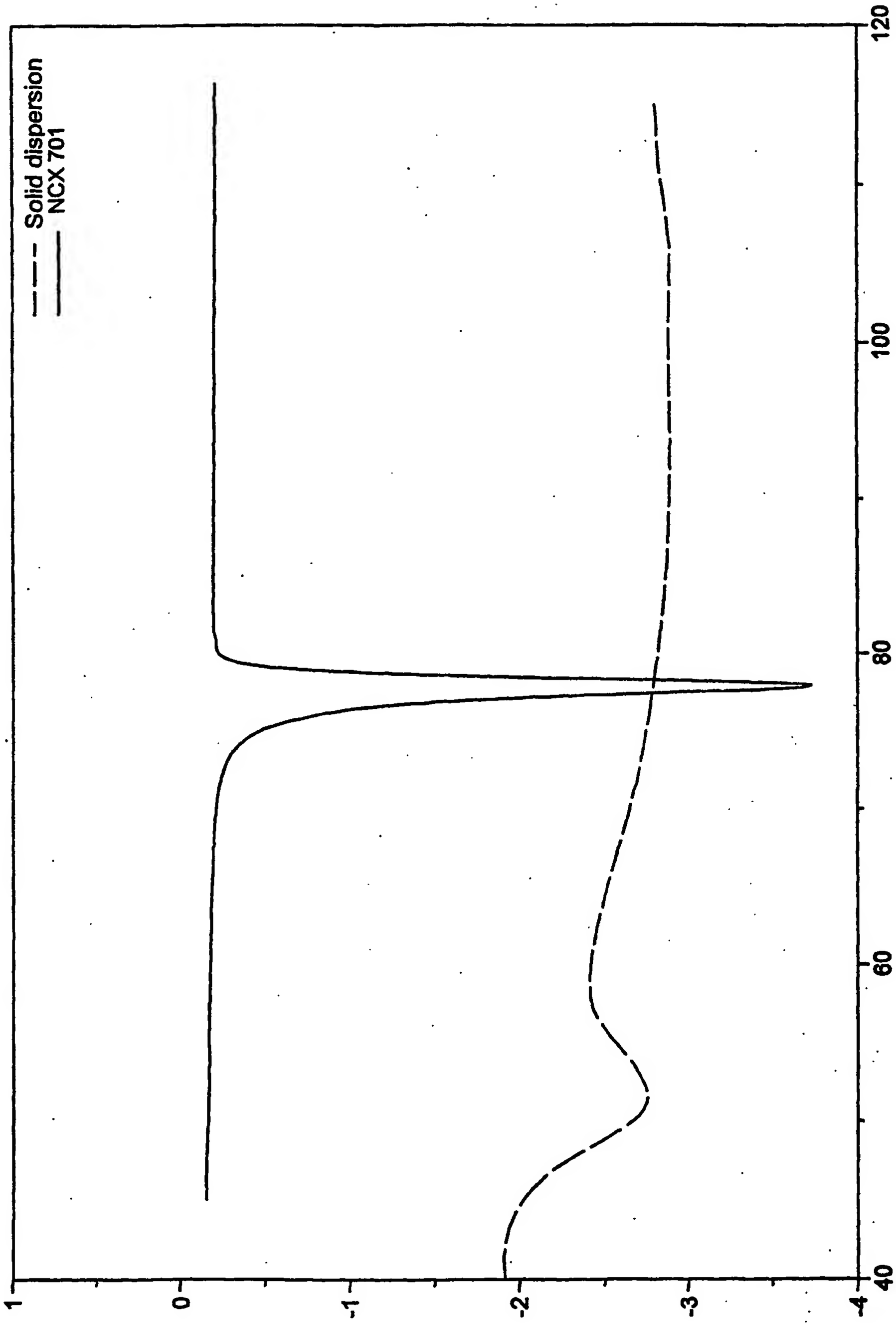

Solid dispersion
NCX 701
Heat Flow (W/g)
1
0
-1
-2
-3
-4
Temperature (°C)
40
60
80
100
120

FIG. 1

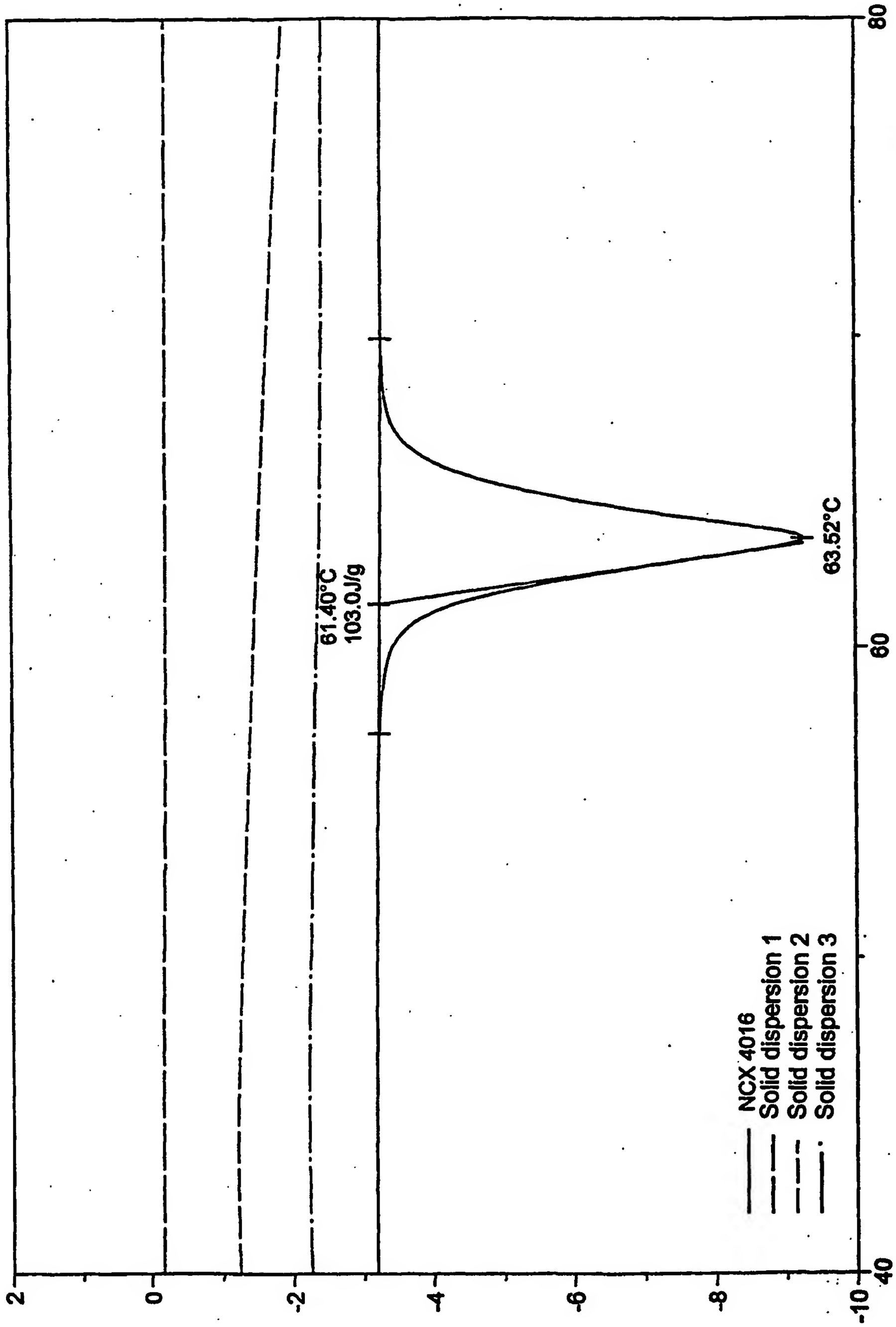

80
60
40
Temperature (°C)
63.52°C
61.40°C
103.0J/g
2
0
-2
-4
-6
-8
-10
Heat Flow (W/g)
NCX 4016
Solid dispersion 1
Solid dispersion 2
Solid dispersion 3

FIG. 2

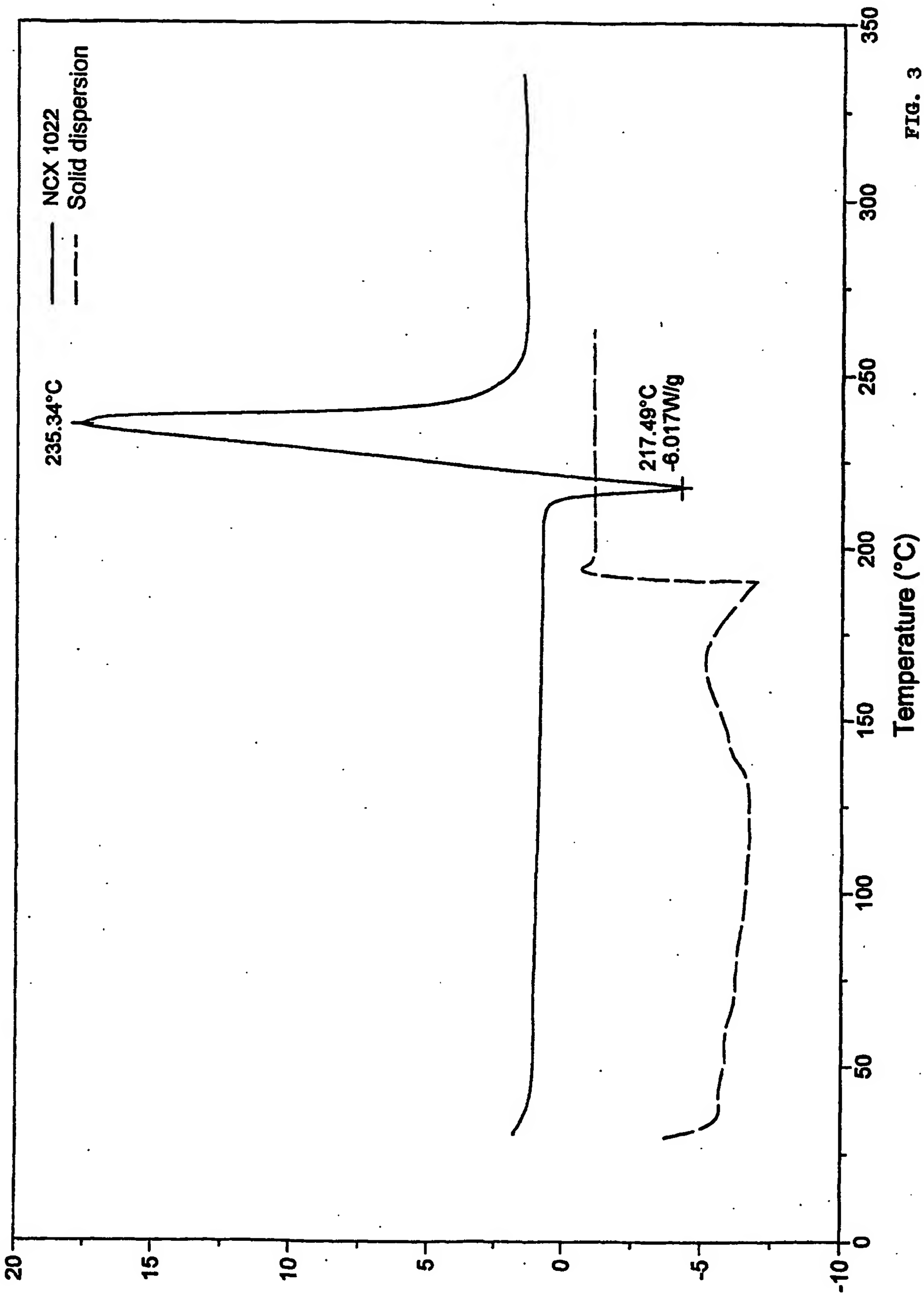

NCX 1022
Solid dispersion
235.34°C
217.49°C
-6.017W/g
Heat flow (W/g)
Temperature (°C)
20
15
10
5
0
-5
-10
0
50
100
150
200
250
300
350

FIG. 3

INTERNATIONAL SEARCH REPORT

Ir I Application No
PCT/EP 01/14967

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MINGHETTI, P.; ET AL.: "Application of solubility parameter in nitroflurbiprofen topical semisolid formulations" PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS 27TH, 7 - 13 July 2000, pages 936-937, XP002199487 Paris (FR)	1,5,9,14
Y	page 936; example 2; table 1	1
P,Y	WO 01 15677 A (ALCON LABORATORIES) 8 March 2001 (2001-03-08) claims 1,7,10,11 page 10, line 6 - line 17 page 14, line 1 - line 8	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2002	06/06/2002

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INTERNATIONAL SEARCH REPORT

information on patent family members

Int nal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0115677 A	08-03-2001	AU 6917400 A	26-03-2001
		WO 0115677 A2	08-03-2001

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Published:
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WO 01/12584 A2

(54) Title: PHARMACEUTICAL COMPOUNDS

(57) Abstract: Compounds or their salts of general formula (I): A-B-N(O)$_s$ wherein: s is an integer equal to 1 or 2; A = R-T$_1$-, wherein R is the drug radical and T$_1$ = (CO)$_t$ or (X)$_{t'}$, wherein X = O, S, NR$_{1c}$, R$_{1c}$ is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -T$_B$ -X$_2$-O- wherein T$_B$ = (CO) when t = 0, T$_B$ = X when t' = 0, X being as above defined; X$_2$, bivalent radical, is such that the precursor drug of A and the precursor of B meet respectively the pharmacological tests described in the description.

PHARMACEUTICAL COMPOUNDS

The present invention relates to novel drugs for systemic use and non systemic use, and the composition thereof, to be used in oxidative stress and/or endothelial dysfuntions of moderate intensity.

By oxidative stress it is meant the generation of free radicals or radicalic compounds, which causes injury both of the cell and that of the surrounding tissue (Pathophysiology: the biological basis for disease in adults and children, McCance & Huether 1998 pages 48-54).

By endothelial dysfunctions it is meant those relating to the vasal endothelium. The damage of the vasal endothelium is known as one of those important events that can cause a series of pathological processes affecting various organs and body apparatuses, as described hereinafter (Pathophysiology: The biological basis for disease in adults and children, McCance & Huether 1998 page 1025).

As known, the oxidative stress and/or the endothelial dysfunctions are associated to various pathologies as reported hereinafter. The oxidative stress can also be caused by toxicity of a great variety of drugs, which significantly affects their performances.

Said pathological events are of a chronic, debilitating character and are very often typical of the elderly. As already said, in said pathological conditions the drugs used show a remarkably worsened performance.

Examples of pathological situations caused by the oxidative stress and/or by the endothelial dysfunctions, or present in elderly, are the following:

- For the cardiovascular system: myocardial and vascular ischaemia in general, hypertension, stroke, arteriosclerosis, etc.
- For the connective tissue: rheumatoid arthritis and connected inflammatory diseases, etc.
- For the pulmonary system: asthma and connected inflammatory diseases, etc.
- For the gastrointestinal system: ulcerative and non ulcerative dyspepsias, intestinal inflammatory diseases, etc.

- For the central nervous system: Alzheimer disease, etc.
- For the urogenital system: impotence, incontinence.
- For the cutaneous system: eczema, neurodermatitis, acne.
- The infective diseases in general (ref.: Schwarz-KB, Brady "Oxidative stress during viral infection: A review" Free radical Biol. Med. 21/5, 641-649 1996).

Further, the ageing process can be considered as a true pathologic condition (ref. Pathophysiology: the biological basis for disease in adults and children, pages 71-77).

The known drugs when administered to patients having pathologies associated to oxidative stress and/or endothelial dysfunctions, show a lower activity and/or higher toxicity.

This happens for example for drugs such as the antiinflammatory, cardiovascular drugs, respiratory apparatus drugs, central nervous system drugs, bone system drugs, antibiotics, urogenital, endocrine drugs, etc.

Drug research is directed to find new molecules having an improved therapeutic index (efficacy/toxicity ratio) or a lower risk/benefit ratio, also for pathological conditions as those above mentioned, wherein the therapeutic index of a great number of drugs results lowered. In fact in the above mentioned conditions of oxidative stress and/or endothelial dysfunctions, many drugs show a lower activity and/or higher toxicity.

For instance antiinflammatory drugs, such as NSAIDs and anticolitic drugs, such as 5-aminosalicylic acid and its derivatives, show the following drawbacks. NSAIDs result toxic particularly when the organism is debilitated or affected by morbid conditions associated to oxidative stress. Said conditions are for example the following: age, pre-existing ulcer, pre-existing gastric bleeding, debilitating chronic diseases such as in particular those affecting cardiovascular, renal apparatuses, the haematic crasis, etc. ("Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. A randomized, double blind, placebo-controlled trial." F.E. Silverstein et Al., Ann. Intern. Med. 123/4, 241-9, 1995; Martindale 31a ed. 1996, pag. 73, Current Medical Diagnosis and Treatment 1998, pages 431 and 794).

The administration of anti-inflammatory drugs to patients

in the above mentioned pathological conditions can be made only at doses lower than those used in therapy in order to avoid remarkable toxicity phenomena. Thus anti-inflammatory activity results poor.

Beta-blockers, used for the angina, hypertension and cardiac arrhythmia treatment, show side effects towards the respiratory apparatus (dyspnoea, bronchoconstriction), and therefore they can give problems in patients affected by pathologies to said organs (asthma, bronchitis). Therefore beta-blockers further worsen respiratory diseases such as asthma. Therefore in asthmatic patients reduced doses of said drugs must be used in order not to jeopardize even more the respiratory functionality. Thus the efficacy of the beta-blockers results very reduced.

Antithrombotics, such as for example dipyridamole, aspirin, etc., used for the prophylaxis of thrombotic phenomena, have the same drawbacks. In patients affected by pathologies connected to oxidative stress and/or endothelial dysfunctions, the therapeutic action or the tolerability of these drugs, as in the case of aspirin, is greatly reduced.

Bronchodilators for example salbutamol, etc., are used in the asthma and bronchitis treatment and drugs active on the cholinergic system are used in pathologies such as urinary cholinergic incontinence. Their administration can produce similar side effects affecting the cardiovascular apparatus, causing problems both to cardiopathic and to hypertensive patients. Cardiopathies and hypertension are pathologies associated, as above said, to the oxidative stress and/or endothelial dysfunctions. Also these drugs show the same drawbacks as those above mentioned.

Expectorant and mucolytic drugs, which are used in the therapy of inflammatory states of the respiratory organs, show drawbacks in patients affected by the above described conditions. Their administration can give rise to heartburn and gastric irritability, particularly in the elderly.

Bone resorption inhibitors, such as diphosphonates (for example alendronate, etc.) are drugs showing high gastrointestinal toxicity. Therefore also these drugs can show the same drawbacks as those above mentioned.

Phosphodiesterase inhibitors, such as for example sildenafil, zaprinast, used in the cardiovascular and respiratory system diseases, are charaterized by similar problems as to tolerability and/or efficacy in the mentioned pathological conditions of oxidative stress and/or endothelial disfunctions.

Antiallergic drugs, for example cetirizine, montelukast, etc. show similar problems in the mentioned pathological conditions, particularly for that it concerns their efficacy.

Anti-angiotensin drugs, f.i. ACE-inhibitors, for example enalapril, captopril, etc., and receptor inhibitors, for example losartan, etc., are used in the cardiovascular disease treatment. Their drawback is to give side effects to the respiratory apparatus (i.e. cough, etc.) in the above mentioned pathological conditions.

Antidiabetic drugs, both of the insulin-sensitizing and of hypoglycaemizing type, such as for example sulphonylureas, tolbutamide, glypiride, glyclazide, glyburide, nicotinamide etc., are ineffective in the prophylaxis of diabetic complications. Their administration can give side effects, such as for example gastric lesions. These phenomena become more intense in the pathological conditions above mentioned.

Antibiotics, for example ampicillin, clarihtromycin, etc., and antiviral drugs, acyclovir, etc., show problems as regards their tolerability, for example they cause gastrointestinal irritability.

Antitumoral drugs, for example doxorubicine, daunorubicin, cisplatinum, etc., have high toxicity, towards different organs, among which are stomach and intestine. Said toxicity is further worsened in the above mentioned pathologies of oxidative stress and/or endothelial dysfunctions.

Antidementia drugs for example nicotine and colino-mimetics, are characterized by a poor tolerability especially in the above mentioned pathologies.

Drugs having a steroidal structure which are used in the therapy of acute diseases (asthma, etc.) or chronic diseases (intestinal, hepatic, respiratory diseases, female reproductive apparatus diseases, hormonal dysfunctions, cutaneous diseases, etc.) are characterized by remarkable toxic effects affecting

various organs, particularly in the above mentioned oxidative stress conditions.

This class of steroidal drugs, among which hydrocortisone, cortisone, prednisone, prednisolone, fludrocortisone, desoxi-corticosterone, methylprednisolone, triamcinolone, para-methasone, betamethasone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, beclomethasone, acetoxy-pregnelone, etc., has remarkable farmaco-toxicological effects on various organs and for this reason the clinical use and its interruption cause a series of side effects, some of which very serious. See for example Goodman & Gilman, "The pharmaceutical Basis of Therapeutics" 9°ed., pag. 1459-1465, 1996.

Among these toxic effects it can be mentioned: those affecting the bone tissue leading to an altered cellular metabolism and high osteoporosis incidence; those affecting the cardiovascular system generating hypertensive responses; those affecting the gastrointestinal apparatus giving gastric damages.

See for example Martindale "The extrapharmacopoeia", 30th ed., pag. 712-723, 1993.

Also biliary acids, which are used in hepatic trouble therapy and in biliary colics, belong to steroidal drugs. The ursodesoxycholic acid is also used in some hepatic troubles (hepatic cirrhosis of biliary origin, etc.). Their tolerability is strongly worsened in the presence of gastrointestinal complications (chronic hepatic damage, peptic ulcer, intestinal inflammation, etc.). Also in the case of biliary acids the oxidative stress notably affects the product performance: both the efficacy and the tolerability of the chenodeoxycholic and ursodesoxycholic acids are meaningfully reduced. In particular the undesired effects affecting liver result exalted. Among steroidal structures also estrogens used for the dislipidaemia, hormonal troubles, female apparatus tumours treatment can be mentioned. Also these steroids show side effects as above mentioned, in particular at hepatic level.

According to the above mentioned prior art, it seems almost impossible to separate therapeutic actions from side effects, see Goodman et al, above mentioned, at p. 1474.

The need was felt to have available drugs showing an

improved therapeutic performance, i.e. endowed both of a lower toxicity and/or higher efficacy, so that they could be administered to patients in morbid conditions of oxidative stress and/or endothelial dysfunctions of moderate intensity, without showing the drawbacks of the drugs of the prior art.

It has now surprisingly and unexpectedly found that the aforementioned problems evidenced following the administration of drugs, to patients affected by oxidative stress and/or endothelial dysfucntions, or to the elderly in general, are solved by a novel class of drugs as described hereinafter.

An object of the invention are compounds or their salts having the following general formula (I):

$$A—B—N(O)_s \qquad (I)$$

wherein:

s is an integer equal to 1 or 2, preferably s = 2;

A = $R—T_1-$, wherein

R is the drug radical and

$T_1 = (CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 6 carbon atoms, or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = $-T_B—X_2—O-$ wherein

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above defined;

X_2, bivalent radical, is such that the corresponding precursor of B does not meet test 5 and meets test 4A; said precursor having formula $-T_B—X_2-OH$, wherein T_B = (CO) and t = 0, the free valence of T_B is saturated with:

-OZ wherein Z = H or R_{1a}, R_{1a} being linear or branched when possible C_1-C_{10} alkyl, preferably C_1-C_5, or with $-Z^I-N(Z^{II})-$, Z^I and Z^{II} being equal or different from each other, having the Z values, when T_B = X and t' = 0, the free valence of T_B is saturated with H;

with the proviso that:

the drug A = $R—T_1-$, wherein the free valence is saturated as hereinafter mentioned:

- when t' = O with:
  - O-Z wherein Z = H or R_{1a} as above defined, or with
  - Z^{I}-N-Z^{II}, (with Z^{I} and Z^{II} being as above defined,
  - when t = 0 with X-Z, wherein X and Z as above defined,

is such as to meet at least one of tests 1-3;

- wherein test 1 (NEM) is a test in vivo carried out on four groups of rats (each formed by 10 rats), the controls (two groups) and the treated (two groups) of which one group of the controls and one group of the treated respectively are administered with one dose of 25 mg/kg s.c. of N-ethylmaleimide (NEM), the controls being treated with the carrier and the treated groups with the carrier + the drug of formula A = R-T_1- wherein the free valence is saturated as above indicated, administering the drug at a dose equivalent to the maximum one tolerated by the rats that did not receive NEM, i.e. the highest dose administrable to the animal at which there is no manifest toxicity, i.e. such as to be symptomatologically observable; the drug complies with test 1, i.e. the drug can be used to prepare the compounds of general formula (I), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in the group treated with NEM + carrier + drug are observed gastrointestinal damages greater than those of the group treated with the carrier, or of the group treated with the carrier + drug, or of the group treated with the carrier + NEM;
- wherein test 2 (CIP) is a test in vitro wherein human endothelial cells from the umbilical vein are harvested under standard conditions, then divided into two groups (each group replicated five times), of which one is treated with a mixture of the drug 10^{-4} M concentration in the culture medium, the other group with the carrier; then cumene hydroperoxide (CIP) having a 5 mM concentration in the culture medium is added to each of the two groups; the drug meets test 2, i.e. the drug can be used to prepare the compounds of general formula (I), if a statistically significant inhibition of the apoptosis (cellular damage) induced by CIP is not obtained with $p < 0.01$ with respect to the group treated with the carrier and CIP;

- wherein test 3 (L-NAME) is a test in vivo carried out on four groups of rats (each group formed by 10 rats) for 4 weeks and receiving drinking water, the controls (two groups) and the treated (two groups), of which one group of the controls and of the treated respectively receives in the above 4 weeks drinking water added of N-ω-nitro-L-arginine methyl ester (L-NAME) at a concentration of 400 mg/litre, the controls in the 4 weeks being administered with the carrier and the treated in the 4 weeks with the carrier + the drug, administering the carrier or the drug + carrier once a day, the drug being administered at the maximum dose tolerated by the group of rats not pretreated with L-NAME, i.e., the highest dose administrable to animals at which no manifest toxicity appears, i.e. such as to be symptomatologically observable; after the said 4 weeks, the water supply is stopped for 24 hours and then sacrified, determining the blood pressure 1 hour before sacrifice, and after sacrifice of the rats determining the plasma glutamic pyruvic transaminase (GPT) after sacrifice, and examining the gastric tissue; the drug meets test 3, i.e. the drug can be used to prepare the compounds of general formula (I), when in the group of rats treated with L-NAME + carrier + drug, greater hepatic damages (determined as higher values of GPT) and/or gastric and/or cardiovascular damages (determined as higher values of blood-pressure) are found in comparison respectively with the group treated with the carrier alone, or with the group treated with the carrier + drug, or with the group treated with the carrier + L-NAME;

- wherein test 4A which must be met by the compound precursor of B is a test in vitro wherein a portion of an erythrocite suspension formerly kept at 4°C for 4 days, said erythrocytes isolated by standard procedures from Wistar male rats and suspended in a physiological solution buffered at pH 7.4 with phosphate buffer, is centrifuged at 1000 rpm for 5 minutes and 0.1 ml of the centrifuged erythrocytes are diluted with sodium phosphate buffer pH 7.4 at 50 ml; aliquots of 3,5 ml each (No. 5 samples) are taken from said diluted suspension and incubated at 37°C in the presence of cumene hydroperoxide at a concentration 270 µM and the suspension turbidity determined at 710 nm at intervals of 30 minutes to establish

the time (Tmax) at which occurs the maximum turbidity, that corresponds to the maximum amounts of cells lysed by cumene hydroperoxide (haemolysis assumed to be = 100%); then alcoholic solutions of the compounds precursors of B are added to 3.5 ml aliquots of the diluted suspension of centrifuged erythrocytes (tests carried out on 5 samples for each precursor of B assayed) in order to have a final concentration 2 mM of the precursor of B and then the resulting suspension preincubated for 30 minutes, cumene hydroperoxide is added in a quantity to have the same above indicated final concentration and at Tmax is determined the percentage of haemolysis inhibition in the sample from the ratio, multiplied by 100, between the absorbance of the sample containing the erythrocytes, the precursor of B and cumene hydroperoxide respectively and that of the sample containing the erythrocytes and cumene hydroperoxide; the precursors of B meet the test if they inhibit the haemolysis induced by cumene hydroperoxide by a percentage > 15%;

- wherein test 5 which must not be met by the precursor compound of B is an analytical determination carried out by adding aliquots of 10^{-4} M methanol solutions of the precursor of B, to a solution formed by admixing a 2 mM solution of desoxyribose in water with 100 mM of phosphate buffer and 1 mM of the salt $Fe^{II}(NH_4)_2(SO_4)_2$; after having thermostatted the solution at 37°C for one hour are added, in the order, aliquots of aqueous solutions of trichloroacetic acid 2.8% and of thiobarbituric acid 0.5 M, heating is effected at 100°C for 15 minutes and the absorbance of the tested solutions is then read at 532 nm; the inhibition induced by the precursor of B in the confront of radical production by Fe^{II} is calculated as a percentage by means of the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound and the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage as above defined of the precursor of B is higher than or equal to 50%;

provided that in formula (I) when X_2 of B is a linear or branched C_1 - C_{20} alkylene or a cycloalkylene having from 5 to